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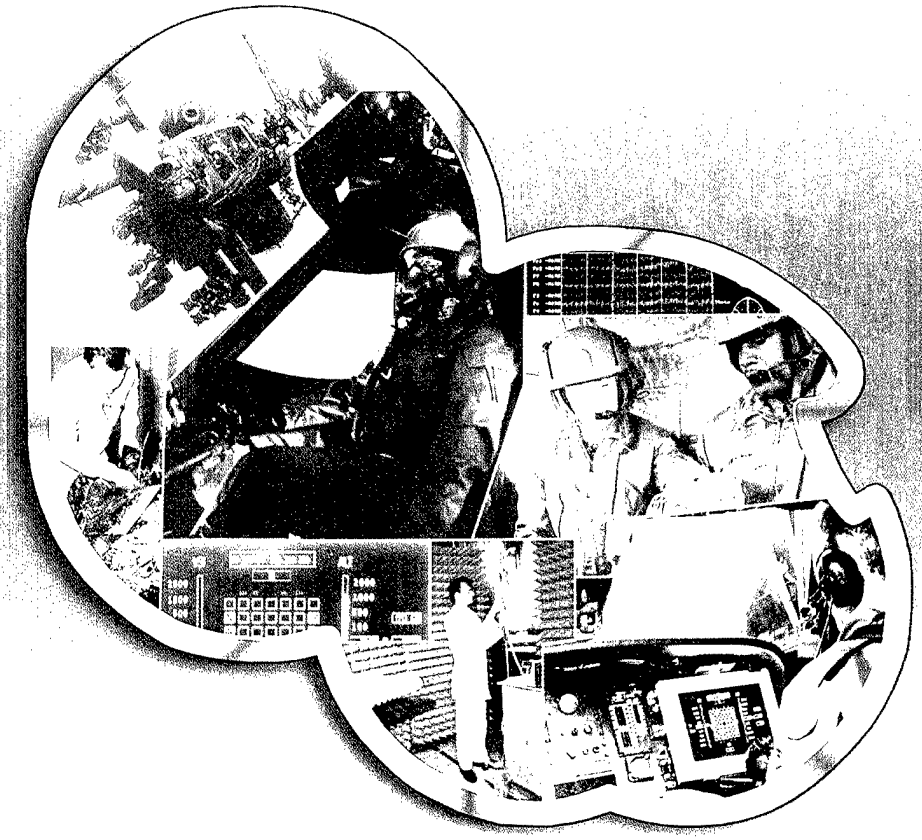
The Efficacy of Temazepam for Improving Daytime Sleep and Nighttime Performance in Army Aviators

by
J. Lynn Caldwell, Kecia K. Hall, Brian F. Prazinko, David N. Norman, Terri Rowe, Bradley S. Erickson, Arthur Estrada, and John A. Caldwell



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Army personnel are commonly rotated to a night shift, or reverse cycle, in order to have the 24-hour period manned at all times. Working reverse cycle presents problems to personnel due to the difficulty in maintaining alertness during the nighttime hours. This is especially difficult when the shift must be worked several consecutive nights, creating a cumulative sleep dept. Appropriate countermeasures are required to ensure that personnel obtain as much rest and sleep as possible during the time required to adjust to reverse cycle so they may perform their duties effectively.

The first objective of this protocol was to determine whether a short-acting hypnotic, taken by an aviator before daytime sleep, would improve sleep quality as measured by objective and subjective means. The second objective was to determine whether improved daytime sleep would increase alertness, reduce fatigue, and mitigate the usual performance decrements which occur during a night shift, particularly when night duty extends over several nights. The third objective was to determine whether improved daytime sleep would

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affect the ability of the body's rhythm to adjust to reverse cycle more rapidly than when daytime sleep is left on its own.

Sixteen U.S. Army aviators between the ages of 22 and 45 were recruited from Fort Rucker, Alabama, and other Army installations. Subjects were randomly assigned to either a temazepam or a placebo group with the constraint that only eight subjects per drug group were allowed. each subject completed several test sessions which consisted of cognitive batteries, flight simulation, sleepiness and electrophysiological evaluations, and mood state questionnaires. Subjects were tested during three baseline days, during three nights of reverse cycle, and during three days following return to day shift (recovery days). The subjects in the temazepam group received 30 mg of temazepam before daytime sleep, while those in the placebo group received a lactose-filled capsule.

Temazepam was successful in improving daytime sleep compared to placebo. Subjects in the temazepam group slept longer and had less fragmentation than those subjects in the placebo group. Generally, the subjects in the temazepam group indicated more subjective alertness and less fatigue than those subjects in the placebo group, as measured by questionnaire and the psychomotor vigilance task (PVT). However, the objective measure of alertness, the Repeated Test of Sustained Wakefulness (RTSW), indicated higher sleepiness levels in the temazepam group than in the placebo group. The temazepam may have residual effects during the night such that when people are placed in an environment which is highly conducive to sleep, the ability to fight drowsiness is not strong enough to prevent sleep from occurring. Flight performance was not affect by improved daytime sleep, possibly due to the early time of the last flight. If testing had continued into the later morning hours, more effects may have been evident in the flight. Physiologically, the circadian rhythm was not altered in this short time span, regardless of the quality or quantity of sleep which occurred during the day. However, fatigue was more evident on the recovery days for the placebo group when compared to the temazepam group. This information is important since it would appear that the cumulative fatigue occurred more slowly for those who had better daytime sleep than for those who were less rested.

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Objectives

The first objective of this protocol was to determine whether a short-acting hypnotic, taken by an aviator before daytime sleep, would improve sleep quality as measured by objective and subjective measures. The second objective was to determine whether improved daytime sleep would increase alertness, reduce fatigue, and mitigate the usual performance decrements which occur during a night shift, particularly when night duty extends over several nights. The third objective was to determine whether improved daytime sleep would affect the ability of the body's rhythm to adjust to reverse cycle (night shift) more rapidly than when daytime sleep is left on its own. Cognitive and flight performance, mood, sleepiness levels, and physiological parameters were measured to address these objectives.

Military relevance

To gain and maintain a tactical advantage on the modern battlefield, Army units must be capable of operating 24 hours per day. Through such continuous operations, the strain upon enemy forces is maximized by requiring a sustained response from both equipment and personnel. However, unless the Army effectively manages all of its resources, the tactical advantage can be lost because of soldier fatigue and the resultant performance impairments.

During such times, some personnel are rotated to a night shift so the 24-hour period will be manned at all times. Night shift (or reverse cycle) in itself presents problems to personnel who must be alert in order to carry out their duties. Anyone who has worked this shift is aware of the difficulty maintaining alertness during the night, particularly when the shift must be worked several consecutive nights. The initial period of adjustment from days to nights is particularly a problem since work still must be accomplished, but the human body is not capable of changing its internal sleep/wake rhythms quickly. Pilots are responsible for planning missions, flying aircraft, managing flight personnel, and performing a host of other duties while on reverse cycle and are faced with completing the mission even during this adjustment time. Sleepiness and fatigue can lead to dangerous consequences for all concerned. Thus, appropriate countermeasures are required to ensure that aviators obtain as much rest and sleep as possible during the time required to adjust to reverse cycle so they may perform their duties effectively.

One countermeasure is to offer pilots opportunities to enhance their ability to sleep during the day, which should lead to better performance when working at night. Research suggests that when daytime sleep is improved by lengthening the amount and preventing fragmentation of sleep, performance during the night shift improves. Daytime sleep, particularly at the beginning of the reverse cycle, is poor, leading to sleep deprivation over a course of time. One way to improve daytime sleep is to administer a short-acting hypnotic that will help maintain sleep, but not interfere with alertness during the night. However, research is necessary before practical guidance for using this countermeasure can be established for the aviation community.

Background

Shiftwork in industrialized countries is very common, with over 22 million people in America working a shift outside the normal day shift (American Sleep Disorders Association, 1994). According to a recent survey of U.S. Army aviation units, approximately 96% of the people surveyed indicated they worked night shift at some point in their career (Caldwell, Gilreath, and Norman, 1999). Research indicates that the problems associated with shift work, particularly night shift, includes disturbed daytime sleep, and fatigue and sleepiness on the job (Akerstedt and Gillberg, 1982; Akerstedt, 1988; Penn and Bootzin, 1990; Härmä, 1995). The reasons for these problems arise from the fact that the human body is programmed to be active during the day and to sleep at night (diurnal). Difficulties occur when one attempts to change these internal rhythms.

The main reason difficulties occur when working at night is due to the body's rhythms of sleep and alertness. Trying to sleep when the body's physiological arousal levels are rising is the main problem associated with daytime sleep. Most research indicates that daytime sleep is approximately 1 to 2 hours shorter than nighttime sleep (Tilley et al., 1982). While a person coming home from the night shift may have no problems initiating sleep, maintaining this sleep as long as desired is difficult at best. Early awakenings, paired with the feeling of unrefreshing sleep, are very common with day sleepers (Akerstedt and Gillberg, 1982). This shortened sleep accumulates during the course of the night shift period, increasing performance problems at night. Studies indicate that after 1 week on night duty, the night worker is functioning at the equivalent of a day worker with 1 night of sleep loss (Tilley et al., 1982).

Trying to stay alert during the time when the body's physiological signals are readied for sleep is a second problem associated with night work. The physiological tendency to sleep at night and to be awake during the day is powerful, with most research indicating that at least a week is needed for the majority of people to change their internal rhythms (Monk, 1986). Some research indicates that even permanent night workers do not adjust completely to night shift (Czeisler et al., 1990). The circadian rhythm is dictated mainly by the light/dark cycle and includes such physiological parameters as temperature, hormone secretions, and heart rate (Minors and Waterhouse, 1990). For example, high body temperature, heart rate, and blood pressure are associated with increased alertness and performance. Decreases in temperature, blood pressure, and cortisol occur in the evening, with a rise in the morning before we awaken (Minors and Waterhouse, 1990). These fluctuations in various body rhythms generally occur whether we are asleep or awake. When the body's signals indicate sleep, as occurs at night, the increase in sleepiness leads to decreases in performance.

These performance decrements which occur during night work are due not only to the physiological tendency to sleep during this time in the 24-hour cycle, but also from the accumulated sleep debt which occurs over the course of nights worked. Research indicates that as the number of nights accumulate for consecutive night duties, accidents increase and productivity decreases Knauth, 1995). A study by Vidače et al., (1986) found an increase in performance from the first to the third night of the shift, which they interpreted as circadian adjustment, but a decrease in performance occurred by the fifth night, attributable to the accumulated sleep dept. Among

strategies which are used to help alleviate some of these problems is improving daytime sleep. Many techniques are suggested which may lead to better daytime sleep (Stone and Turner, 1997). These include environmental changes such as earplugs to mask out noise, eyeshades to block out light, etc. While these are somewhat helpful, daytime sleep is still shorter and less restful than desired.

Another technique to improve daytime sleep is the use of hypnotics. Most sleep aids are helpful in promoting sleep during the day with very few, if any, effects on sleep architecture (Stone and Turner, 1997). However, the choice of hypnotics is crucial to the success of this technique. If the hypnotic is too short, then sleep maintenance will suffer. If it is too long, then hangover effects will mask any improvement to performance and alertness that may have occurred with improved daytime sleep. Temazepam is a hypnotic which may be beneficial to improve daytime sleep since its half-life is approximately 8 hours and it has no active metabolites (Breimer, 1979).

Promoting daytime sleep with temazepam

In some situations, aviation personnel may be able to improve their daytime sleep with the aid of a hypnotic. While there are many circumstances where this is not possible (when call to duty may be imminent, or there is only a short time available for sleep, making a sleep aid too long to be beneficial), there are some times when a sleep aid would improve daytime sleep. This improved sleep may lead to a decrease in nighttime sleepiness associated with sleep dept and help the person adjust to night shift. A potential hypnotic, which has been shown to improve daytime sleep and have little or no hangover effects, is temazepam.

General characteristics

Temazepam, marketed by Novartis Pharmaceuticals as Restoril, is an intermediate-acting benzodiazepine hypnotic. It is supplied in 7.5, 15, and 30 mg capsules for oral administration. It is indicated for the short-term treatment of insomnia (Physicians' Desk Reference, 2000).

The hypnotic efficacy of temazepam has been proven many times over, showing improvements in sleep maintenance by reducing the number of awakenings during the night with no significant effects on sleep architecture, particularly in the 30 mg dose (Mitler et al., 1979). It has also been shown to improve daytime sleep objectively as well as subjectively (Porcù et al., 1997; Donaldson and Kennaway, 1991).

Pharmacokinetics

Temazepam is an intermediate-acting benzodiazepine with a mean elimination half-life of 8.8 hours. Peak plasma levels ranging from 666-982 ng/mL (mean of 865 ng/mL) occurred on the average 1.5 hours post-dose (Physicians' Desk Reference, 2000). Daytime absorption is faster, and the half-life and peak plasma time is slightly shorter than it is at night (Müller et al., 1987).

Approximately 92% of temazepam is metabolized with 80% excreted in the urine; no major active metabolites are present (Schwarz, 1979).

Safety

Temazepam has been shown to be a safe drug (Fillingim, 1979). In studies conducted with rats, no effects were found on fertility in males or females, however, an increased risk of congenital malformations is associated with temazepam during the first trimester of pregnancy, and therefore, should not be taken by women who are pregnant. In addition, temazepam should be administered with caution in severely depressed individuals or in those with evidence of latent depression (Physicians' Desk Reference, 2000). In studies in which temazepam was administered for 7 consecutive nights, no increases in plasma concentrations were found, indicating that repetitive drug administration is safe and effective (Breimer, 1979).

Adverse reactions

The most common central and peripheral nervous system adverse reactions include drowsiness, headache, fatigue, nervousness, lethargy, dizziness, hangover, and anxiety; the most common gastrointestinal reactions are nausea and diarrhea (Roth and Roehrs, 1991). The Physicians' Desk Reference indicates that memory disturbance is rare (less than 0.5%). Research comparing temazepam with triazolam indicates that, while triazolam may show anterograde amnesia, no impairment was observed with temazepam (Scharf, Fletcher, and Graham, 1988).

Sleep architecture

Research indicates that 15 and 30 mg of temazepam delayed rapid eye movement (REM) sleep latency by an average of 32 minutes compared to placebo, but did not suppress total REM sleep. The amounts of stages 3 and 4 sleep decreased from the first night to the second night after the 30 mg dose of temazepam, however, the authors did not indicate the amount of this decrease (Roth et al., 1979).

Dosage

The beginning recommended dosage is 15 mg, but 30 mg may be needed for some patients. Research indicates that 15 mg, while effective in some people, does not produce consistent hypnotic effects, while 30 mg is consistent (Roth et al., 1979).

Tolerance and toxicity

There is mixed evidence concerning the tolerance of temazepam. Some have shown no evidence of tolerance to 30 mg of temazepam for up to 7 weeks (Allen et al., 1987; Mitler et al., 1979), while others have shown tolerance with 15 mg (Kales et al., 1986). Rebound insomnia (defined as a worsening of sleep compared to baseline) has been reported after 14 nights of a 30-mg dose, but not after the 15-mg dose. However, after several weeks' use of both the 15- and 30-mg

doses, studies have shown symptoms of rebound insomnia characterized by an increased sleep latency and wake time and decreased total sleep time after abrupt discontinuation of the drug (Roth and Roehrs, 1991).

The oral dose in which 50 percent of subjects lived (LD_{50}) was 1963 mg/kg in mice, 1833 mg/kg in rats, and >2400 mg/kg in rabbits. In cases of overdose, the Physicians' Desk Reference recommends vomiting induced mechanically or with emetics, or, if unconscious, gastric lavage used concurrently with a cuffed endotracheal tube. Maintenance of adequate pulmonary ventilation is required. Flumazenil administration may be used with measures taken to secure airway, ventilation, and intravenous access.

Performance and hangover effects

Very few studies have shown impairment in cognitive and motor performance during morning tests after 30 mg nighttime administration of temazepam (Nicholson, 1979). Most studies show no morning performance decrements after 30 mg or less of temazepam. Roth et al. (1979) found that 30 mg of temazepam did not affect next-day alertness or performance. These findings were supported by other research (Mattila et al., 1984; Wesnes and Warburton, 1984; 1986). Wesnes and Warburton (1986) found that daytime administration of 10 and 20 mg of the soft capsule temazepam did not affect nighttime performance. Porcú et al. (1997) supported these findings.

Study questions

Research indicates that temazepam can enhance daytime sleep, and some research has shown that improved daytime sleep attenuates the performance decrements associated with nighttime performance. The ability of aviators to take advantage of hypnotics to improve their daytime sleep will depend upon the effects of the hypnotics on performance.

The first question addressed by this study was whether 30 mg of temazepam taken before daytime sleep would improve objective and subjective sleep quality. The second question addressed was whether improved daytime sleep would attenuate the decrements in nighttime performance of aviators who are on reverse cycle for several nights. The final question addressed was whether improved daytime sleep would lead to a faster adaptation to reverse cycle when compared to a natural daytime sleep.

Methods

Subjects

Sixteen UH-60 Army aviators between the ages of 22 and 45 were recruited from Fort Rucker, Alabama, and other Army installations. All potential subjects were given a full explanation of all procedures involved in participation and signed an informed consent. Subjects were screened for current significant medical problems (including sleep abnormalities), use of tobacco products, current use of medications (other than sodium naproxin, ibuprofen, acetaminophen, or aspirin) that

could not be discontinued, or excessive use of caffeine (no more than three 8-ounce cups caffeinated coffee or five 12-ounce caffeinated soft drinks per day). Two subjects used tobacco and were allowed to smoke during breaks, but not during the test session. A blood sample was taken from the female volunteer and tested to ensure she was not pregnant. Medical evaluations were conducted by a flight surgeon prior to testing. Subjects were instructed to abstain from drug and alcohol use for 48 hours prior to the beginning of the study, and no drug or alcohol use was permitted during participation, except as noted above. Subjects remained inside of the U.S. Army Aeromedical Research Laboratory (USAARL) at Fort Rucker, Alabama, for the duration of testing (10 consecutive days and 9 nights).

Apparatus

Subjective circadian evaluations

Daily sleep diaries (see Appendix A) were completed by some of the subjects prior to reporting to the laboratory, however, most subjects were not compliant with this request. The purpose of these data was to determine the person's individual sleep/wake habits and help in the interpretation of their data collected during the study.

The Horne and Östberg Morningness/Eveningness Questionnaire (Horne and Östberg, 1976) was used to subjectively evaluate each subject's circadian type. This 19-item questionnaire is a paper-and-pencil test which asks questions concerning bedtime and risetime preferences. It has been shown that circadian type may affect one's ability to quickly adjust to night shift (Åkerstedt, 1988; Härmä, 1995).

Mood evaluation

The Profile of Mood States (POMS) (McNair, Lorr, and Droppleman, 1981) was used to assess subjective reports of mood at various times throughout the test sessions. This paper-and-pencil questionnaire consists of 65 items which measure affect on 6 scales: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. The original questionnaire was programmed for computer administration and scoring.

Sleepiness evaluations

Visual Analog Scale (VAS). Subjective sleepiness was measured via the VAS which consists of eight 100 mm lines centered over the adjectives "alert/able to concentrate", "anxious", "energetic", "feel confident", "irritable", "jittery/nervous", "sleepy", and "talkative" (Penetar et al., 1993). At the extremes of each line, "not at all" and "extremely" are printed, respectively. Scores consist of the distance of the subject's mark from the left end of the line (in mm). This questionnaire was presented on a computer screen and scored by a computer program.

Repeated Test of Sustained Wakefulness (RTSW). An objective measure of alertness was obtained using the RTSW (Hartse, Roth, and Zorick, 1982) in which the subject's

electroencephalogram (EEG) was recorded for up to 20 minutes using a Grass electroencephalograph (Model No. 8 Plus*) during the test to objectively determine whether or not the subject successfully remained awake. Subjects were awakened and removed from the room immediately if they showed signs of stage 2 sleep. Records were scored visually in terms of the number of minutes from lights out until the first indication of Stage 2 sleep (up to 20 minutes).

Simulator performance

All simulator flights were conducted on site at the USAARL facility using the USAARL UH-60 research flight simulator. This motion-base system includes an operational crew station, computer-generated visual display, environmental conditioning (set at a constant cockpit temperature of 72 degrees F and a humidity of 70%), and a multi-channel data acquisition system. Flight data were acquired on a DEC VAX 11/780* interfaced to a Perkin-Elmer digital computer which controls the UH-60 flight simulator. This system is capable of monitoring any aspect of simulator control, from heading, airspeed, and altitude, to global positioning system (GPS) readouts, switch positions, and operator console inputs. For the purposes of this investigation, only 17 channels of data were monitored. The acquired data were stored on the DEC VAX 11/780 and transferred after each flight to a DEC VAX 11/785. Flight performance scores, including root mean square (RMS) errors, were derived using specialized software routines developed in the Laboratory (Jones and Higdon, 1991). The flight score data were subsequently examined with standard statistical procedures.

The flight performance evaluations required subjects to perform the profile described in Table 1. The same sequence of maneuvers was used for every subject during each of the flights. These maneuvers are of the type typically flown in a UH-60 aircraft, and they are fully described in the Aircrew Training Manual (ATM). The entire profile lasted approximately 54 minutes, during which performance was measured using the simulator's computerized performance monitoring system. Each maneuver was scored for parameters such as airspeed, altitude, slip, roll, etc. Each maneuver, along with the parameters to be measured, is listed in Table 2. During each flight, the console operator (a UH-60 pilot) was present to instruct the subject and ensure the proper sequencing of all flight maneuvers. In addition, the console operator marked the beginning and ending point of each individual maneuver for the purpose of delimiting subsequent computer scoring. He also informed the subject about the maneuver to be flown and marked the start point of the maneuver when the subject was instructed to initiate that maneuver.

Cognitive evaluations

Multi-Attribute Test Battery (MATB). The MATB is a computerized aviation simulation test requiring subjects to perform an unstable tracking task while concurrently monitoring warning lights and dials, responding to auditory requests to adjust radio frequencies, and managing simulated fuel flow rates. This computerized test is controlled by a Pentium computer equipped with a standard keyboard, a joystick, and a mouse. Data on tracking errors, response times, time-outs, false alarms, and accuracy rates are calculated automatically by computer.

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* See manufacturers' list

Table 1.
Flight maneuvers.

Maneuver	Description
1. Straight climb	Climb from 2000 to 4000 ft maintaining hdg and airspeed
2. Straight & level	Maintain track of 178, alt 4000 ft, airspeed 120 k for 2 min
3. Straight & level	Maintain track of 230, alt 4000 ft, airspeed 120 k for 3 min
4. Straight climb	Climb from 4000 to 5500 ft maintaining hdg and airspeed
5. Straight descent	Descend from 5500 to 4000 ft maintaining hdg and airspeed
6. Rt std rate turn	Perform 180 right turn maintaining hdg and airspeed
7. Straight & level	Maintain hdg of 240, alt 4000 ft, airspeed 120 k for 2 min
8. Rt desc turn	Perform 360 right turn while descending from 4000 to 3000 ft
9. Straight & level	Maintain hdg of 240, alt 3000 ft, airspeed 120 k for 2 min
10. Rt desc turn	Perform 180 right turn while descending from 3000 to 2500 ft
11. Straight descent	Descend from 2500 to 1000 ft maintaining hdg and airspeed
12. Lt climb turn	Perform 180 left turn while climbing from 1000 to 1500 ft
13. Straight climb	Climb from 1500 to 3000 ft maintaining hdg and airspeed
14. Rt climb turn	Perform 360 right turn while climbing from 3000 to 4000 ft
15. Straight & level	Maintain hdg of 240, alt 4000 ft, airspeed 120 k for 2 min
16. Lt desc turn	Perform 360 left turn while descending from 4000 to 3000 ft
17. Instrument Landing System (ILS)	Execute ILS approach

Psychomotor Vigilance Task (PVT). The PVT, a portable simple reaction time test known to be sensitive to sleep loss (Dinges et al. 1997), visually displays numbers which increment rapidly until the subject responds (Computer Science & Applications, Inc.*). The stimulus is presented for up to 1.5 seconds, allowing the subject to respond. The subject presses a microswitch which allows reaction time to the stimulus light to be recorded. The interstimulus interval varies randomly from 1 to 10 seconds. The data are stored on computer for future analysis.

Waking EEG evaluations

EEGs were collected with a Cadwell Spectrum 32 neurometric analyzer. The data from seven active electrode sites (Fz, C3, Cz, C4, Pz, O1, and O2) referenced to linked mastoids (A1 and A2) were collected and stored on an optical disk for future analysis. The low filter was set at 0.53 Hz, the high filter was set at 70 Hz, and the 60 Hz notch filter was used. Grass E5SH silver cup electrodes were attached to each subject's scalp with collodion for the duration of the study.

Table 2.
Maneuvers with parameters scored.

Maneuver	Parameters	Ideal Values
Climb	Track	178
	Airspeed	80 knots
	Slip	0 ball position
	Roll	0 degrees
	Rate of climb	1000 feet/minute
Straight and level	Track	178
	Altitude	4000 feet MSL
	Airspeed	120 knots
	Roll	0 degrees
Straight and level	Track	230
	Altitude	4000 feet MSL
	Airspeed	120 knots
	Roll	0 degrees
Climb	Track	351
	Airspeed	120 knots
	Slip	0 ball position
	Roll	0 degrees
	Rate of climb	500 feet/minute
Descent	Track	351
	Airspeed	120 knots
	Slip	0 ball position
	Roll	0 degrees
	Rate of descent	500 feet/minute
Right standard rate turn	Turn rate	3 degrees/second
	Altitude	4000 feet MSL
	Airspeed	120 knots
	Slip	0 ball position
	Roll	20 degrees
Straight and level	Heading	240 degrees
	Altitude	4000 feet MSL
	Airspeed	120 knots
	Roll	0 degrees
Right descending turn	Turn rate	3 degrees/second
	Airspeed	120 knots
	Slip	0 ball position
	Roll	20 degrees
	Rate of descent	500 feet/minute
Straight and level	Heading	240 degrees
	Altitude	3000 feet MSL
	Airspeed	120 knots
	Roll	0 degrees
Right descending turn	Turn rate	3 degrees/second
	Airspeed	120 knots
	Slip	0 ball position
	Roll	20 degrees
	Rate of descent	500 feet/minute

Table 2 (continued)

Maneuver	Parameters	Ideal Values
Descent	Track	060
	Airspeed	120 knots
	Slip	0 ball position
	Roll	0 degrees
	Rate of descent	500 feet/minute
Left climbing turn	Turn rate	3 degrees/second
	Airspeed	120 knots
	Slip	0 ball position
	Roll	20 degrees
	Rate of climb	500 feet/minute
Climb	Heading	240 degrees
	Airspeed	120 knots
	Slip	0 ball position
	Roll	0 degrees
	Rate of climb	500 feet/minute
Right climbing turn	Turn rate	3 degrees/second
	Airspeed	120 knots
	Slip	0 ball position
	Roll	20 degrees
	Rate of climb	500 feet/minute
Straight and level	Heading	240 degrees
	Altitude	4000 feet MSL
	Airspeed	120 knots
	Roll	0 degrees
Left descending turn	Turn rate	3 degrees/second
	Airspeed	120 knots
	Slip	0 ball position
	Roll	20 degrees
	Rate of descent	500 feet/minute

Physiological data

Temperature. Core body temperature was collected with a CorTemp personal heat stress monitor which contains a temperature sensor inside a pill which is swallowed. The radio pill telemeters temperature data to a monitor worn on the belt. The sampling rate is 2 hertz. Data are stored by the monitor and downloaded to a standard computer every 24 hours. The pill travels through the digestive tract and is passed by the subject after approximately 24 hours. The person swallowed a new pill each day or after the pill was no longer detectable so that core temperature could be monitored throughout the 24-hour day.

Hormones. Saliva samples were collected throughout the testing period using Sali-savers (American Laboratory Products Company (ALPCO)). Samples were immediately stored at –20° C until future analysis in which melatonin and cortisol were measured with an enzyme-linked immunosorbent assay (ELISA). Melatonin analyses were performed using Bühlman direct-saliva kits and cortisol analyses via Milenia direct-saliva adapted kits (ALPCO). Standard chemistry

laboratory equipment was used along with an ALPCO plate rotator, a Tecan Columbus automated plate washer, and a Tecan Spectra Classic plate reader (ALPCO).

Polysomnography

Evaluations of sleep architecture during each sleep period were made using a Grass electroencephalograph (Model No. 8 Plus). The EEG data from electrodes C3, C4, O1, and O2, referenced to contralateral mastoids (A1 or A2) were recorded. Eye movements (electrooculogram (EOG)) were assessed with electrodes affixed to the outer canthus of each eye and referenced to A1. Muscle activity (electromyogram (EMG)) was recorded from submental electrodes affixed with adhesive collars. The time constant for the EEG channels was 0.3 second, and the high filter was 35 Hz. For EOG, the time constant was 5.0 seconds, and the high filter was 10 Hz. For EMG, the time constant was 0.003 second, and the high filter was 120 Hz. The 60 Hz notch filter was used as necessary.

Light levels

Wrist activity monitors (WAM) (Ambulatory Monitoring, Inc.*) were worn throughout the testing period. These monitors recorded movement of the subjects as well as the light exposure. While activity was not the major factor of concern, light exposure was important. Data from the WAM were downloaded to a computer every 24 hours and stored for future analysis. Light exposure was determined for each subject throughout the study and used as a factor in the analysis if the two drug groups had different levels of light exposure.

Procedure

Each subject completed several test sessions which consisted of cognitive batteries, flight simulation, sleepiness and electrophysiological evaluations, and mood state questionnaires. Subjects were tested during baseline, during a reverse cycle period, and a return to day shift (recovery days), a total of 9 days of testing. Subjects were randomly assigned to either the temazepam or the placebo group with the constraint that only eight subjects per drug group were allowed. Subjects signed an informed consent before the study began.

Mood evaluation

The POMS was administered every 2 hours, beginning at 0900 on training, baseline, and recovery days and at 1700 on reverse cycle days. Additional tests were administered immediately before retiring for the sleep period (both day and night) and immediately upon awakening. The last administration occurred at 2245 on baseline and recovery days, and at 0645 on reverse cycle days. The test was administered using a computerized version of the standard POMS answer sheet. Subjects indicated how well each of 65 adjectives described the way they were feeling at the time by marking a line with the computer cursor. The test took approximately 5 minutes.

Sleepiness evaluations

VAS. The VAS was administered every 2 hours immediately after the POMS, beginning at 0900 on training, baseline, and recovery days, and beginning at 1700 on reverse cycle days. Additional tests were administered immediately before retiring and immediately upon awakening. The subject was administered the test via a computer screen; a series of 100 mm lines were presented horizontally over the adjectives described earlier. At the extremes of each line, "not at all" and "extremely" were printed, respectively. The subject placed a mark with the cursor on the line to indicate his/her present feelings.

RTSW. The RTSW occurred every 3 hours. Subjects were required to lie on a bed in a quiet, darkened room after being instructed as follows: "lie as still as possible with your eyes closed and do your best to remain awake." During the RTSW, EEG data were recorded from electrode sites C3, C4, O1, and O2, referenced to the contralateral mastoid. The subject was allowed to remain in bed either until 20 minutes had elapsed or until he/she entered stage 2 sleep (the first K complex or sleep spindle). The elapsed time from lights out until sleep onset was recorded.

Simulator performance

Subjects flew the flight protocol described in Tables 1 and 2 every 3 hours, beginning at 1000 on the training, baseline days, and recovery days, and at 1800 on reverse cycle days. This flight profile consisted of a route flown from Cairns Army Airfield to Enterprise Airport, included a missed approach into Enterprise, and a return to Cairns Army Airfield where the pilot landed using an ILS approach.

There were 17 maneuvers in the profile, consisting of 3 climbs, 4 straight-and-levels, 2 descends, 1 right standard rate turn, 2 right descending turns, 1 left climbing turn, 1 right climbing turn, 1 left descending turn, and an ILS approach. During each of the upper airwork maneuvers, the subjects were required to maintain an airspeed of 120 knots, but the specific targets for other parameters such as heading, altitude, roll, slip, etc. changed depending upon which maneuver was flown. However, subjects always attempted to maintain appropriate ideal flight parameters during each maneuver.

The computer calculated scores for a variety of measures within each of the flight maneuvers in order to express how well subjects maintained specific headings, altitudes, airspeeds, and other parameters. The entire flight lasted approximately 54 minutes. Each flight was coordinated and controlled by one of the console operators who instructed the subjects through the standardized maneuvers in a uniform fashion. Console operators maintained a quiet environment in the cockpit throughout each flight. They refrained from discussing the effects of night work or sleeping medications on performance, and from making comparisons between volunteers even if such information was solicited. In addition, console operators did not provide any feedback to volunteer pilots regarding the accuracy of performance, the procedures used, or specific or general techniques designed to improve or in any way change performance because coaching may influence the subjects' behavior in unpredictable ways. Console operators avoided answering specific questions

asked by subjects about their performance or technique by stating that they would provide the subject with a full debrief at the end of the study. The only exception regarding the prohibition on feedback was that on the training day, the console operator provided any training necessary to bring the subject as close to full proficiency as possible.

Cognitive evaluations

MATB. Subjects completed the MATB every 3 hours from 0930 to 1730 on training, baseline, and recovery days, and from 1730 to 0130 on reverse cycle days. The test followed the completion of the POMS, VAS, RTSW, and simulator flight, and was 20 minutes in length. Subjects were required to simultaneously monitor and respond to four different tasks throughout the testing period. As described earlier, there was a resource management task (monitoring fuel levels), a communications task (adjusting radio frequencies in response to verbal commands), a systems monitoring task (monitoring lights and dials), and an unstable tracking task. In the resource management task, subjects were required to maintain 2500 units of "fuel" in 2 tanks by monitoring and controlling the status of 8 "pumps." The communications task required subjects to monitor verbal instructions about radio-frequency changes presented via headphones and respond only to the ones preceded by their unique call sign (NGT504). The systems monitoring task required subjects to attend to two warning lights and four dials and to press specific keys either to terminate the onset of a specific light or to reset a dial deviating more than two tick marks from center. The tracking task required subjects to center an unstable target in the middle of the top right quadrant of the computer screen. Scores on accuracy and speed were recorded automatically by computer.

PVT. Subjects performed the PVT twice every 3 hours beginning at 1100 on training, baseline, and recovery days, and at 1900 on reverse cycle days. The test was paired with the resting EEG which occurred after the simulator flight and again after the MATB, and was 10 minutes in length. In addition, the subjects sat in a chair for one of the PVTs and stood during the other. Whether one sat or stood was counterbalanced among the subjects so that one half of the subjects sat during the first PVT and stood during the second, and one half of the subjects stood during the first PVT and sat during the second. Subjects were required to monitor a screen on which numbers counted up until the subject responded by pressing a button with his/her dominant hand. The stimulus was presented randomly every 1 to 10 seconds and remained on the screen for up to 1.5 seconds, or until the subject responded. Reaction time (RT) was recorded for each stimulus and was analyzed in three ways: 1) the number of reaction times greater than 500 milliseconds (lapses), 2) the overall reaction time, and 3) the fastest 10% reaction times per trial.

Waking EEG evaluations

The electrophysiological evaluations lasted approximately 10 minutes. The sessions occurred twice every 3 hours from 1000 to 1800 on training and recovery days and from 1800 to 0200 on reverse cycle days. As with the PVT, one EEG session was collected while the subject was standing and the other was collected while the subject was sitting. The order of the postures was counterbalanced within subjects. The electrodes were checked before each session to ensure impedances were 5000 Ohms or less. Any problems were corrected by rotating a blunted needle

gently in the electrode until the correct impedance was obtained. The subjects either were seated in a comfortable chair or stood in a quiet test area where they were instructed to remain quiet with eyes open and fixated for 1.5 minutes followed by eyes closed for 1.5 minutes. The data from each resting EEG were visually scanned for three relatively artifact free 2.5-second epochs and fast Fourier transformations were conducted. The averaged epochs produced four power values for each electrode site under eyes closed and eyes open for each posture. The activity bands were delta (1.5-3.0 Hz), theta (3.0-8.0 Hz), alpha (8.0-13.0 Hz), and beta (13.0-20.0 Hz).

Physiological data

Temperature. Core body temperature was continuously recorded throughout the testing period. Subjects swallowed the radio pill at approximately 1600 on the first day in the laboratory, and approximately every 24 hours thereafter. The monitor was checked hourly to determine that data were collected as needed, and the data were downloaded every 24 hours.

Hormones. Saliva samples were collected every 2 hours beginning at 0705 until 2245 on training and baseline days, and from 1505 until 0645 on reverse cycle days. Subjects gave approximately 3 mL of saliva via Sali-savers, after which the samples were stored at –20° C until further analyses (ELISA) were conducted. Samples were extracted from Sali-savers according to manufacturer's instructions and aliquotted as necessary. The ELISAs were conducted according to directions provided by kit manufacturer. The results of the ELISA were submitted to statistical analysis once all data were collected.

Polysomnography

EEG, EOG, and EMG was recorded each sleep period (both day and night) in order to assess sleep quality. Approximately 25 minutes before lights out, EOG and EMG electrodes were placed. The subject then was escorted to a private bedroom where electrodes were plugged into the preamplifiers and signal quality assessed. Afterwards, the lights were turned out and the subject permitted to sleep. The first night of sleep was Monday night (the adaptation night). Tuesday and Wednesday nights served as the baseline sleep nights. Friday and Saturday were day sleep for reverse cycle, and the second Monday and Tuesday nights were recovery nights. Transition to reverse cycle on Thursday included a delay of bedtime until 0700 on Friday. Transition back to days on Sunday included a delay of bedtime until 2300 on the second Monday. Lights out on baseline and recovery nights were 2300; lights out for reverse cycle was 0700. Subjects were allowed to sleep until 0700 on baseline and recovery days, and until 1500 on reverse cycle days. If a subject awakened early and requested to leave bed, he/she was encouraged to return to sleep, but was allowed to arise if he asked after a period of time when no sleep occurred. All sleep data were recorded on standard polygraph paper and scored according to standard procedures (Rechtschaffen and Kales, 1968). Sleep was scored in terms of sleep latency (number of minutes from lights out to the first full minute of stage 2 sleep), percentage of time in each of the sleep stages (1, 2, 3, 4, and REM, latency to REM (number of minutes from sleep onset to the first REM period of 2 minutes or more), movement time, total sleep time, and time awake after sleep onset.

Light levels

A WAM was initialized and strapped on the volunteer's wrist after the electrodes were attached on the first day. Each evening, the data were downloaded, the WAM reinitialized and strapped back on the volunteer's wrist. The amount of time in which light levels were above 200 lux was calculated for each subject. The lux level of 200 was chosen since it is generally accepted that bright light suppresses melatonin secretion at night. No conclusive evidence showed that lower levels of light consistently suppress melatonin secretion (Brainard, Rollag, and Hanifin, 1997). Therefore, dim room light was chosen in order to prevent suppression of melatonin during the night. The light levels of each drug group were determined to assess whether one group was exposed to more light than the other.

Testing schedule

Each subject reported to the Laboratory on Monday afternoon and signed the informed consent prior to medical records review. Collection of the sleep diaries, completion of the Morningness/Eveningness questionnaire, and attachment of electrodes followed. Familiarization to the Laboratory and the first training session occurred prior to the adaptation sleep period, which began at 2300 on Monday night and ended at 0700 on Tuesday morning. On Tuesday, training sessions were completed (0900, 1300, and 1700). During each session, subjects completed all tests in the sequence to be used for the remaining 7 days. Within each session, a saliva sample, the POMS, VAS, and RTSW were completed. The first of the EEG evaluations and the PVT were followed by a simulator flight. After the flight, another saliva sample, POMS, and VAS were completed. Following these, the MATB and the second EEG evaluation and PVT concluded the test session. Subjects slept from 2300-0700 on Tuesday night. On Wednesday and Thursday, baseline days, the schedule was the same as Tuesday except the subject was not permitted to sleep Thursday night. Instead, additional test sessions were conducted at 1700, 2100, and 0100, each a replica of the sessions conducted on baseline days. Sleep began at 0700 on Friday, with either drug or placebo administered at 0630. Subjects were awakened at 1500 to begin the reverse cycle period. If he/she awakened earlier and requested to end the sleep period, he/she was encouraged to stay in bed. However, if he/she requested to arise after not returning to sleep, he/she was permitted to get up and end the sleep period. On Sunday, subjects were not allowed to go to bed, but continued the test schedule as they did on the baseline days (sessions at 0900, 1300, and 1700). At 2300 on Sunday night, the subject was allowed to sleep. Recovery days were on Monday and Tuesday, with test sessions at 0900, 1300, and 1700. After sleeping on Tuesday night, the subjects were debriefed and released by 0900 on Wednesday. See Table 3 for a full schedule of the week and Table 4 for the order within each test session.

Data analysis

The data collected from each independent measure (with the exception of the sleep diaries, the Morningness/Eveningness Questionnaire, and physiological and temperature data) were analyzed with a three-way repeated measures analysis of variance (ANOVA) for drug group (temazepam versus placebo), day (baseline days, reverse cycle days, and recovery days) and session (six total

sessions, three from each day). The "day" factor was determined by when a session occurred rather than a 24-hour day, since some sessions began in the evening of one day and continued into the next day. For example, the first reverse cycle began at 1700 on Thursday and continued until 0600 on Friday. Therefore, the "day" factor is not by 24-hour day, but according to when sessions within a period occurred. The days analyzed included the baseline days (Tuesday and Wednesday), the reverse cycle days (Friday and Saturday), and the recovery days (Monday and Tuesday).

The flight performance data, which included scores for various measures taken during each maneuver, were included in the ANOVA design above plus an iteration factor when a maneuver was flown more than once in a profile. The EEG and PVT analysis also included a posture factor (sitting versus standing). The alpha level was set at 0.05. Huynh-Feldt corrected degrees of freedom were applied in the event of significant departures from the compound symmetry assumption. Significant interactions were followed up with analysis of simple effects, and main effects were assessed with pairwise contrasts among the means, except for the session factor which was followed up with trend analysis since contrasts would have given an excessive number of comparisons.

The sleep diaries were used for informational purposes only and were not statistically analyzed. Only a small portion of the sample (4 of the 16 participants) actually completed the diary, but verbal reports indicated that all participants were able to adapt to the time zone before they entered the study. All participants were within a time zone of no more than 1 hour difference from the central time zone at least 10 days before entering the study.

The results from the Morningness/Eveningness Questionnaire indicated that the majority of the participants scored either moderately morning types (3 in the temazepam group and 4 in the placebo group) or neither type (5 in the temazepam group and 2 in the placebo group). One person in the placebo group scored definitely morning and one person in the placebo group scored moderately evening. Since there were no group differences in this scale, these data were not used for any of the subsequent analyses.

Light exposure above 200 lux was calculated for each subject. Comparisons were made between each drug group to determine if the amount of light exposure was different between the two groups. The average number of minutes of light exposure above 200 lux for the temazepam and placebo groups was 241.6 and 121.6, respectively. The range in the temazepam group was 37 to 936 minutes, and the range in the placebo group was 9 to 289 minutes. The data from the person in the temazepam group with the excessively high number of minutes above 200 lux (936 minutes) were removed from the group average, leaving the mean exposure time for the temazepam group as 142.4 minutes. However, even with all the data included, the difference in exposure between the two groups was not statistically significant. Given this result, the light data were not used further.

Table 3.
Testing schedule.

	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Mon	Tue	Wed
0100		Slp	Slp	Slp	Rev Test 3	Rev Test 6	Rev Test 9	Slp	Slp	Slp
0200		Slp	Slp	Slp				Slp	Slp	Slp
0300		Slp	Slp	Slp				Slp	Slp	Slp
0400		Slp	Slp	Slp	Dinner	Dinner	Dinner	Slp	Slp	Slp
0500		Slp	Slp	Slp	PT/Hyg	PT/Hyg	PT/Hyg	Slp	Slp	Slp
0600		Slp	Slp	Slp	**Dose (0630)**	**Dose (0630)**		Slp	Slp	Slp
0700		Wake	Wake	Wake	BT	BT		Wake	Wake	Wake
0800		Brk	Brk	Brk	Slp	Slp		Brk	Brk	Brk
0900		Trng 2	BL 2	BL 5	Slp	Slp	Rec Test 1	Rec Test 4	Rec Test 7	Release
1000					Slp	Slp				
1100					Slp	Slp				
1200		Lunch	Lunch	Lunch	Slp	Slp	Lunch	Lunch	Lunch	
1300	Arrive Inf Cons M/E Que	Trng 3	BL 3	BL 6	Slp	Slp	Rec Test 2	Rec Test 5	Rec Test 8	
1400					Slp	Slp				
1500	Elect				Wake	Wake				
1600					Brk	Brk				
1700	Trng 1	BL 1	BL 4	Rev Test 1	Rev Test 4	Rev Test 7	Rec Test 3	Rec Test 6	Rec Test 9	
1800										
1900										
2000	Dinner	Dinner	Dinner	Dinner			Dinner	Dinner	Dinner	
2100	PT/Hyg	PT/Hyg	PT/Hyg	Rev Test 2	Rev Test 5	Rev Test 8	PT/Hyg	PT/Hyg	PT/Hyg	
2200										
2300	BT	BT	BT				BT	BT	BT	
2400	Slp	Slp	Slp				Slp	Slp	Slp	

NOTE: Slp – Sleep; Brk – Breakfast; BT – Bedtime; PT/Hyg – Physical training/Hygeine; BL – Baseline; Rec – Recovery; Inf Cons – Informed consent; M/E Que – Morningness/Eveningness Questionnaire.

Table 4.
Test block schedule.

Test	Length in minutes
Saliva sample	2
VAS/POMS	3
RTSW	20
MATB	20
EEG/PVT	20
Simulator Flight	55
Saliva sample	2
VAS/POMS	3
EEG/PVT	20

The saliva samples were frozen after each collection, and batches were analyzed in the USAARL biochemistry laboratory using the ELISA method for analysis of melatonin and cortisol levels. The temperature data were reduced to one value every 15 minutes. The results from the reduced temperature data, along with melatonin and cortisol measures, were visually inspected to find the time of daily peaks. Only the 24 hours of the last day shift and the 24 hours of the last night shift were used in the analysis. The difference between the day shift and the night shift peaks was calculated. These differences were then subjected to a t-test to determine whether a shift from pre-night shift to post-night shift occurred. The difference in peak times were analyzed with a t-test for differences between the two drug groups as well as differences between the times regardless of group.

Results

Mood evaluations

The data from each of the factors from the POMS were analyzed separately with a 3-way ANOVA, including a drug group (temazepam or placebo), day (baseline, reverse cycle, and recovery), and session (18 sessions across both days). The ANOVA revealed a significant interaction among drug group, day, and session for Fatigue ($F(34,476)=1.68$, $p=.0106$). Simple effects analysis revealed significant differences among the days for the placebo group at sessions 1,

2, 6, 7, 8, 9, 15, 16, 17, and 18, and significant differences among the days for the temazepam group at sessions 8 and 9, with a tendency at sessions 16, 17, and 18 (p = .06). Further analyses indicated that fatigue was higher for the placebo group during the reverse cycle days than during the baseline days beginning at session 6 (p=.06) through session 9, then again at session 15 through 18. In addition, fatigue was higher during the reverse cycle days than during the recovery days at sessions 7, 8, and 9 (p=.06), and again at sessions 16, 17, and 18. At sessions 1 and 2, fatigue was higher during the recovery days than during the baseline days. For the temazepam group, fatigue was higher during the reverse cycle days than during the baseline and recovery days at sessions 8 and 9, with a tendency at sessions 16, 17, and 18. No other sessions showed a difference among the days. These effects are shown in Figure 1.

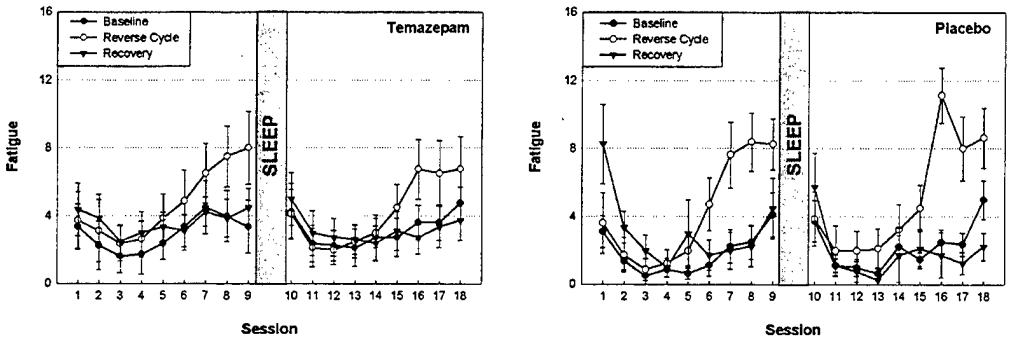

Figure 1. A drug group by day by session interaction for factors from the POMS.

A significant interaction among day and session occurred for Depression (F (34,476)=1.52, p=.0324), Vigor (F(34,476)=6.04, p<.0001), Fatigue (F(34, 476)=8.46, p<.0001), and Confusion (F(34,476)=5.30, p<.0001). Further analyses indicated higher Depression scores on the reverse cycle days than on the baseline and recovery days for sessions 8 (p=.06 for recovery day), 12, 17, and 18; higher scores for Vigor during the baseline days than during the reverse cycle days at sessions 2, 4, 6, 7, 8, 9, 15, 16, 17, and 18, and higher scores during the reverse cycle days than during the recovery days at sessions 7, 8, 9, 15, 16, 17, and 18. The scores were higher for Vigor during the reverse cycle days than on the recovery days at sessions 1, 3, and 10; and higher scores during the baseline days than during the recovery days at sessions 1, 2, 3, 4, 6, and 10. Scores were higher for Fatigue during the reverse cycle days than during the baseline days and the recovery days at sessions 6, 7, 8, 9, 15, 16, 17, and 18; and higher during the recovery days than during the baseline days at sessions 1 and 2. Scores were higher for Confusion during the reverse cycle days than during the baseline days at sessions 6, 7 (p=.06), 8, 9, 15, 16, 17, and 18; and scores were higher during the reverse cycle days than during the recovery days at sessions 7, 8, 15, 16, 17 and 18. Finally, the recovery day scores were higher than the baseline and reverse cycle days at sessions 1 and 10. These differences are depicted in Figure 2.

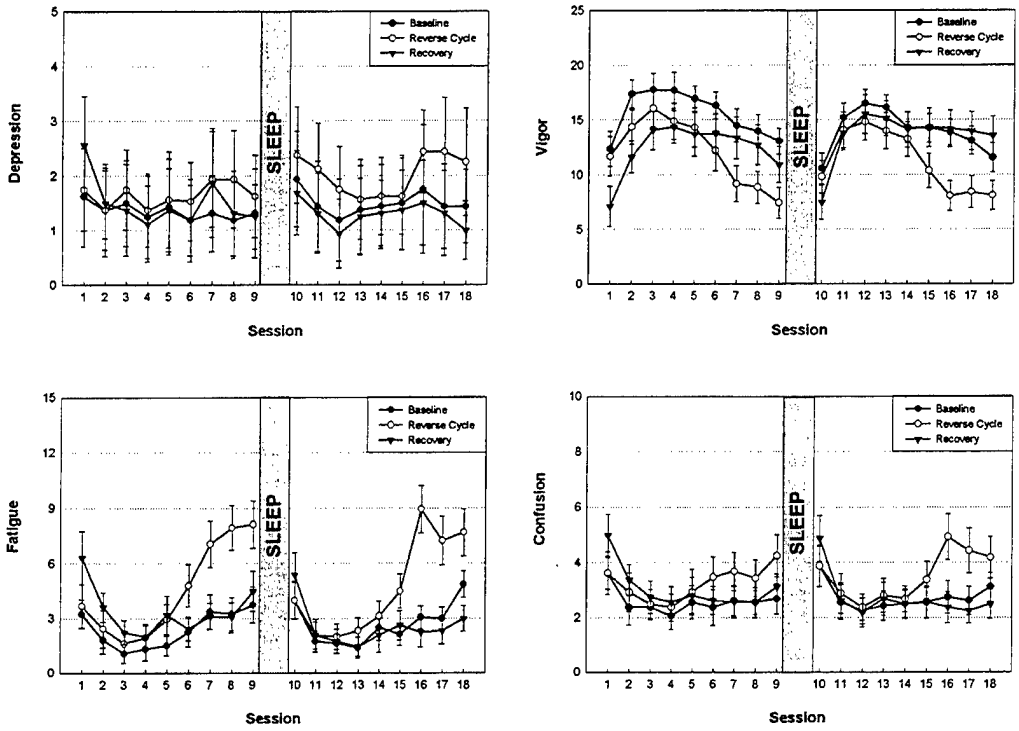

Figure 2. A day by session interaction for factors from the POMS.

Another interaction occurred between session and drug group for Vigor ($F(17,238)=2.52$, $p=.0001$). This effect was due to linear and cubic trends in the sessions for the temazepam group, and quadratic and cubic trends in the sessions for the placebo group. These effects are depicted in Figure 3.

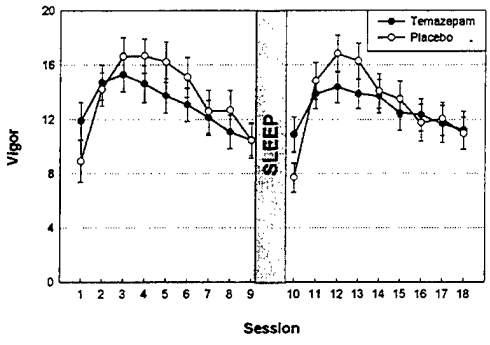

Figure 3. A session by drug group interaction for Vigor from the POMS.

A significant main effect for day occurred for Vigor ($F(2,28)=13.65$, $p=.0001$), Fatigue ($F(2,28)=11.19$, $p=.0003$), and Confusion ($F(2,28)=6.23$, $p=.0058$). This effect occurred because

the scores for Vigor were higher and the scores for Fatigue and Confusion were lower on the baseline days than on the reverse cycle days. Scores also were higher for Vigor on the baseline days than on the recovery days. Also, scores for Vigor were lower and scores for Fatigue were higher on the reverse cycle days than on the recovery days. The means for each of these factors for each day are shown in Table 5.

Table 5.
Means for the day main effects for the POMS.

	Vigor	Fatigue	Confusion
Baseline	14.75	2.55	2.63
Reverse Cycle	11.66	4.58	3.38
Recovery	12.99	2.97	2.89

A significant main effect for session occurred for Tension ($F(17, 238)=1.73$, $p=.0388$), Depression ($F(17,238)=2.77$, $p=.0003$), Anger ($F(17,238)=1.81$, $p=.0273$), Vigor ($F(17,238)=15.25$, $p<.0001$), Fatigue ($F(17,238)=13.26$, $p<.0001$), and Confusion ($F(17,238)=8.64$, $p<.0001$). This effect occurred because of a significant linear trend for Tension, Vigor, and Fatigue. In addition, a significant quadratic trend occurred for Depression, Fatigue ($p=.06$) and Confusion; and a significant cubic trend occurred for Tension, Vigor, Fatigue, and Confusion. The means are shown in Table 6.

Sleepiness evaluations

VAS. The data from the VAS were analyzed with a three-way ANOVA, including drug group (temazepam or placebo), day (baseline, reverse cycle, and recovery), and session (18 sessions across both of the days). The results revealed that a significant interaction occurred among drug group, day, and session for Alertness ($F(34,476)=1.56$, $p=.0243$), Confidence ($F(34,476)=1.46$, $p=.0468$), and Sleepiness ($F(34,476)=1.90$, $p=.0020$). Analyses of simple effects indicated significant differences for Alertness and Sleepiness among the days for the temazepam group at sessions 16 and 17, and for the placebo group at sessions 1, 16, and 17. Further analyses indicated that, for the temazepam group, subjective sleepiness levels were higher and alertness levels were lower during the reverse cycle days than during the baseline and recovery days at both sessions 16 and 17; alertness levels were also lower on the recovery days compared to the baseline days at session 16. Confidence levels were lower at session 17 during the reverse cycle days than during the recovery days. The placebo group indicated lower subjective alertness and confidence levels, and higher subjective sleepiness levels during the reverse cycle days than during the baseline and recovery days at sessions 1 (not alertness), 16, and 17. These effects are depicted in Figure 4.

Table 6.
Means for the session main effects for the POMS.

	Tension	Depression	Anger	Vigor	Fatigue	Confusion
Session 1	3.10	1.98	1.06	10.40	4.42	4.08
Session 2	2.96	1.42	0.65	14.46	2.63	2. 90
Session 3	3.23	1.54	0.65	15.96	1.65	2.54
Session 4	2.75	1.25	0.75	15.65	1.75	2.33
Session 5	3.15	1.46	0.79	14.98	2.54	2.77
Session 6	3.14	1.30	0.69	14.09	3.16	2.82
Session 7	3.77	1.71	0.96	12.35	4.52	2.96
Session 8	3.02	1.48	0.79	11.88	4.75	2.85
Session 9	2.75	1.40	0.56	10.48	5.46	3.35
Session 10	3.65	2.00	1.06	9.29	4.46	4.21
Session 11	3.19	1.63	0.79	14.35	1.96	2.68
Session 12	3.60	1.29	0.60	15.60	1.79	2.27
Session 13	3.52	1.40	0.77	15.08	1.71	2.65
Session 14	3.71	1.46	0.79	13.90	2.56	2.56
Session 15	3.40	1.50	0.71	12.98	3.08	2.83
Session 16	3.81	1.90	1.29	12.04	4.75	3.35
Session 17	3.29	1.73	0.71	11.85	4.19	3.10
Session 18	3.58	1.56	0.85	11.08	5.19	3.27

A significant interaction between day and session was revealed for Alertness ($F(34,476)=6.99$, $p<.0001$), Energy ($F(34,476)=5.25$, $p<.0001$), Confidence ($F(34,476)=3.57$, $p<.0001$), Irritability ($F(34.476)=2.31$, $p=.0001$), Sleepiness ($F(34,476)=7.48$, $p<.0001$), and Talkativeness ($F(34,476)=3.47$, $p<.0001$). The follow-up analyses indicated that scores were lower on Alertness, Energy, Confidence, and Talkativeness during sessions 6, 7, 8, 9, 15, 16, 17, and 18 of the reverse cycle days compared to the baseline and recovery days. Scores on Irritability were higher during sessions 16 and 17 on the reverse cycle days, while scores on Sleepiness were higher during sessions 6, 7, 8, 9, 15, 16, and 17 on the reverse cycle days when compared to the baseline and recovery days. The effects are shown in Figure 5.

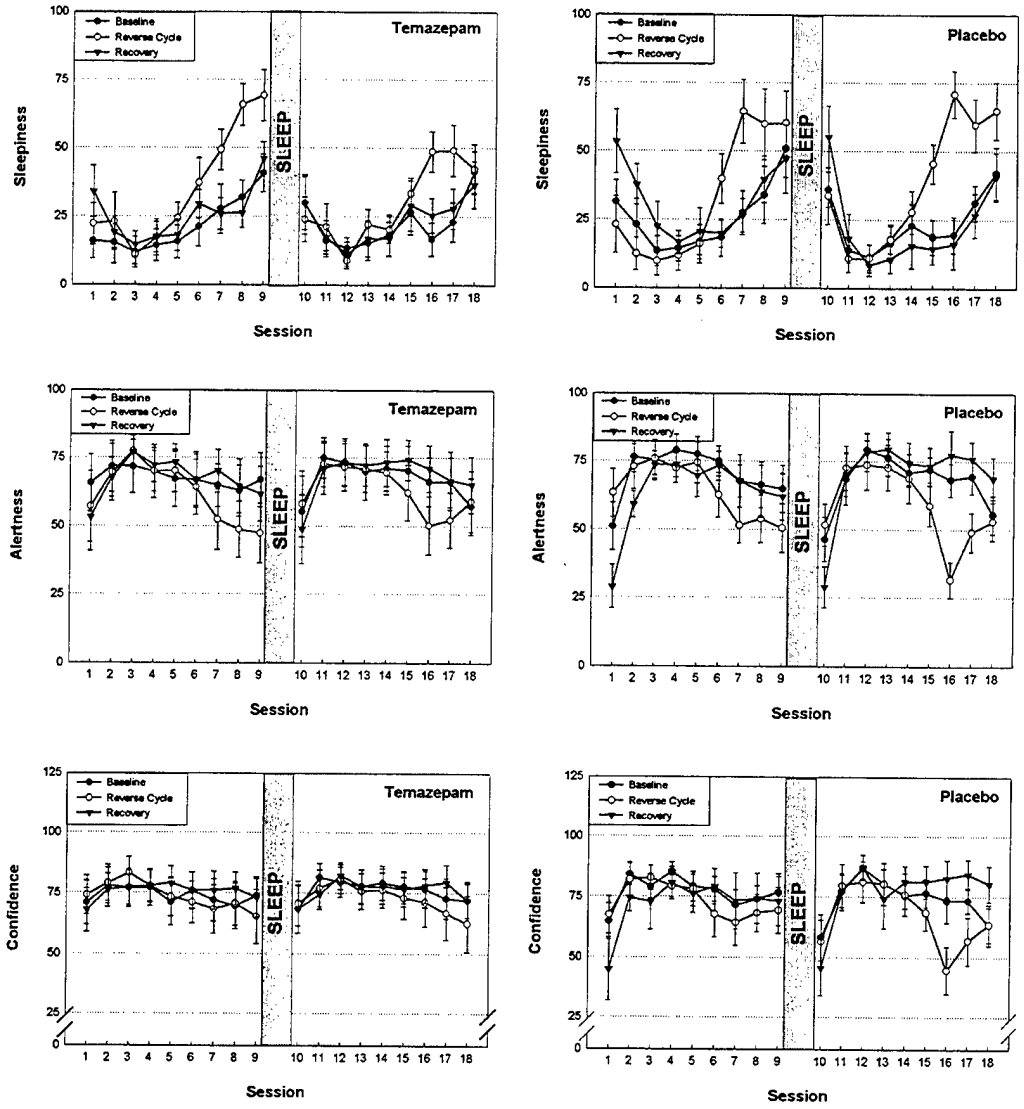

Figure 4. A drug group by day by session interaction for the factors from the VAS.

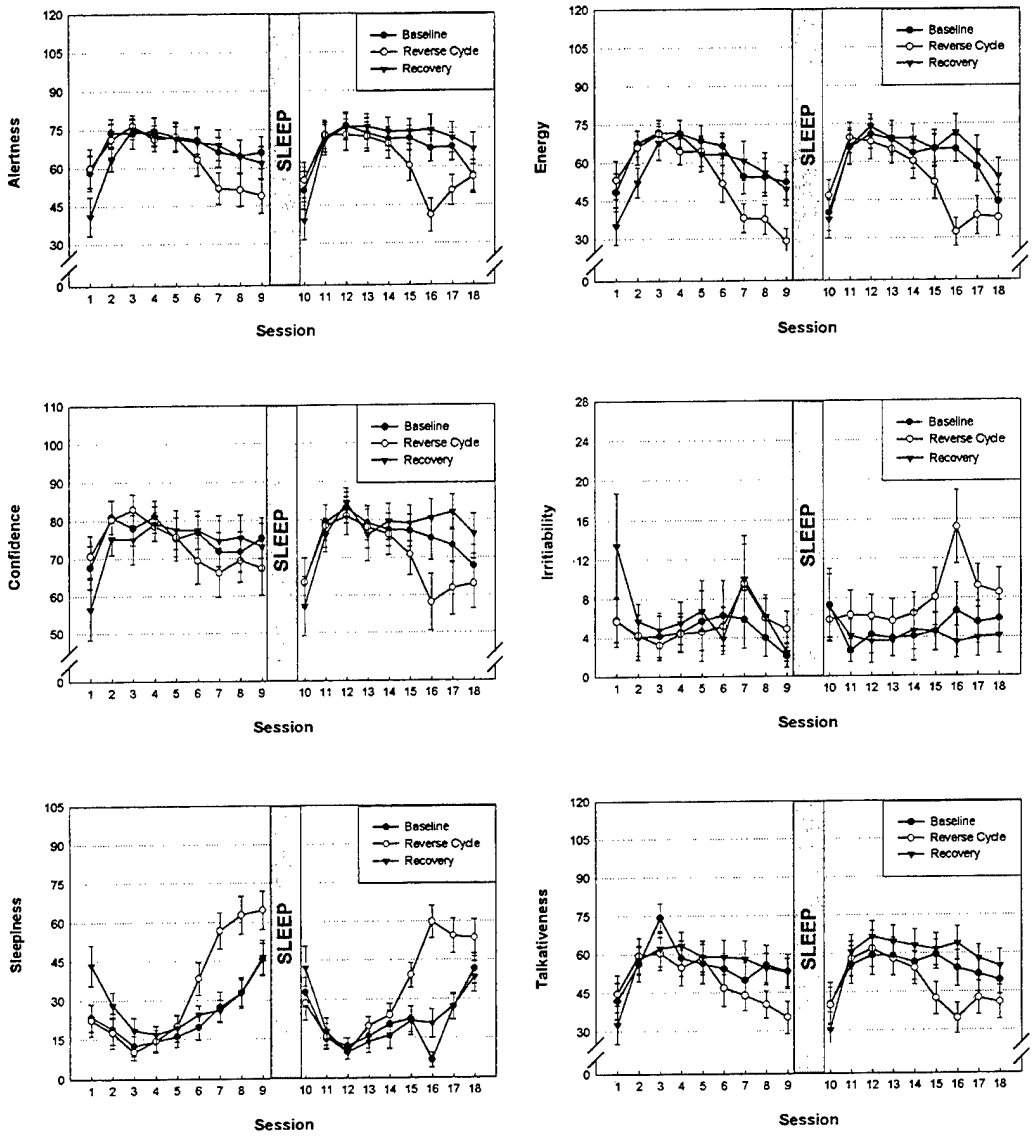

Figure 5. A day by session interaction for factors from the VAS.

An interaction between drug group and session occurred for Energy ($F(17,238)=2.94$, $p=.0001$) and Confidence ($F(17,238)=1.73$, $p=.0391$). Follow-up analyses indicated the temazepam group showed a significant cubic trend in the sessions for Energy, but not for Confidence. The placebo group showed significant cubic trends for both Energy and Confidence. The interaction occurred because the placebo group had lower scores for both factors than the temazepam group at the beginning of each day, but then had similar scores for both groups by the end of each morning. These effects are depicted in Figure 6.

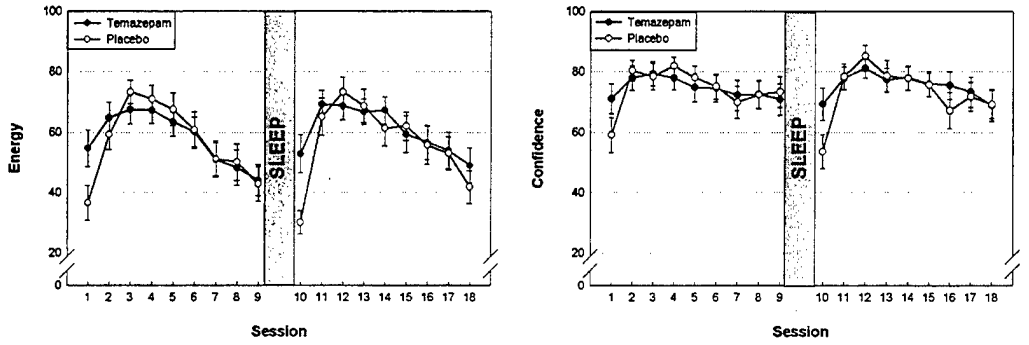

Figure 6. A drug group by session interaction for factors from the VAS.

In addition to significant interactions, significant main effects also occurred. A significant session effect was revealed for Alertness ($F(17,238)=16.37$, $p<.0001$), Energy ($F(17,238)=19.94$, $p<.0001$), Confidence ($F(17,238)=7.02$, $p<.0001$), Irritability ($F(17,238)=2.65$, $p=.0006$), Sleepiness ($F(17,238)=16.53$, $p<.0001$), and Talkativeness ($F(17,238)=10.87$, $p<.0001$). A significant linear trend occurred for Sleepiness. Significant quadratic trends occurred for Alertness, Energy, Confidence, Irritability, with a tendency for Talkativeness ($p=.06$). Significant cubic trends occurred for Alertness, Energy, Confidence, Sleepiness, and Talkativeness. The effects are shown in Figure 7.

Also, a significant day effect occurred for Alertness ($F(2,28)=3.66$, $p=.0388$), Energy ($F(2,28)=9.35$, $p=.0008$), Sleepiness ($F(2,28)=14.15$, $p=.0001$), and Talkativeness ($F(2,28)=7.39$, $p=.0026$). Contrasts among the means for the days indicated Alertness, Energy, and Talkativeness were lower and sleepiness was higher on the reverse cycle days than on the baseline and recovery days. The means are shown in Table 7.

Table 7.
Means for the day main effects for the VAS.

	Alertness	Energy	Sleepiness	Talkativeness
Baseline	68.10	60.96	23.22	54.08
Reverse Cycle	62.02	52.60	34.10	48.76
Recovery	67.26	60.58	25.86	56.91

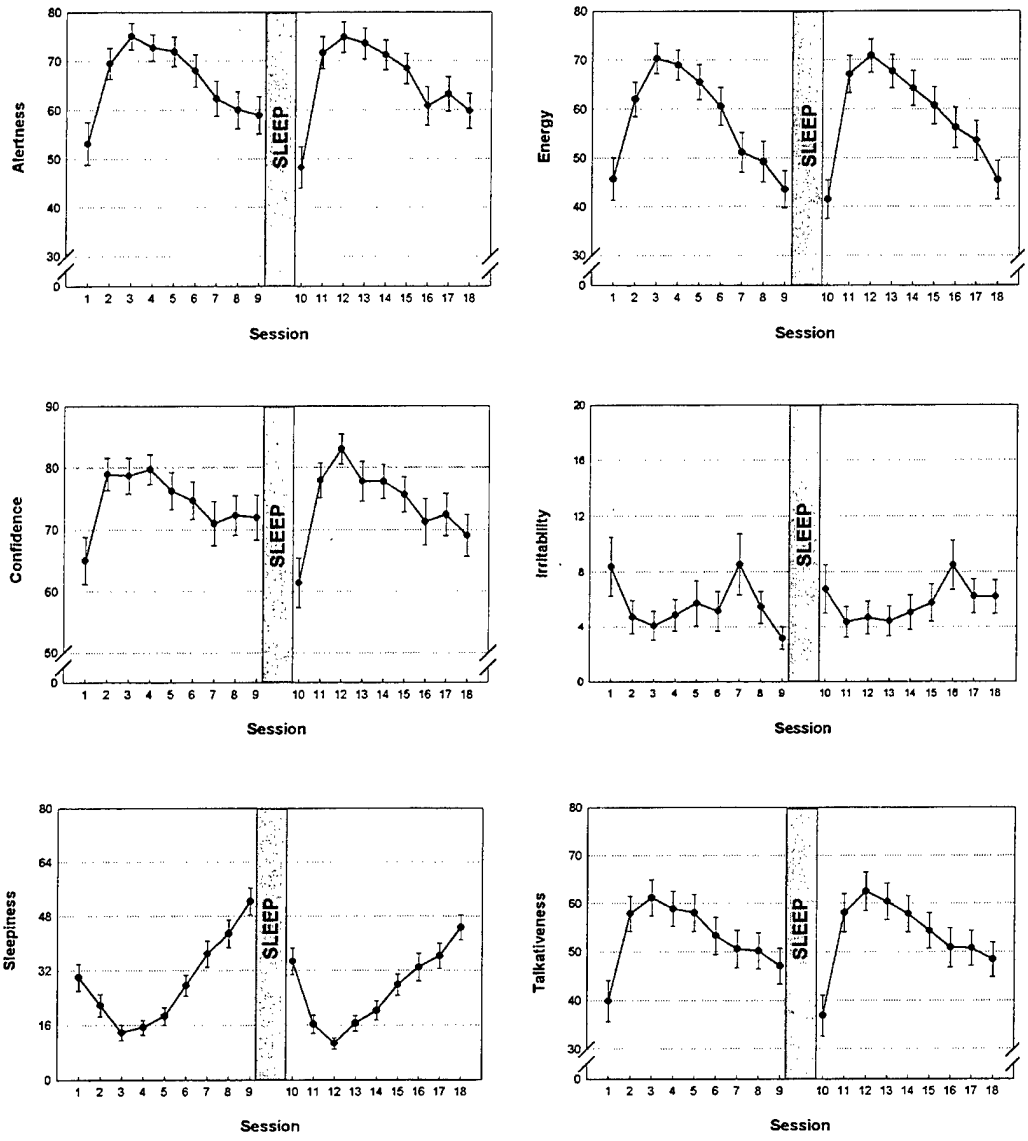

Figure 7. A session effect for factors from the VAS.

RTSW. A mixed factorial ANOVA was used to analyze the minutes to stage 1 sleep and to stage 2 sleep from the RTSW (2 groups by 3 days by 3 sessions). The ANOVA indicated a significant interaction between day and session for minutes to stage 1 sleep ($F(10,140)=5.35$, $p<.0001$) and for minutes to stage 2 sleep ($F(10,140)=3.90$, $p=.0001$). Follow-up simple effects and contrasts indicated significantly shorter latency to stage 1 during the baseline compared to the reverse cycle days at sessions 1 and 2, with minutes to stage 2 showing significant at session 2 only. There was also a significantly shorter latency to stage 1 during the recovery days compared to the reverse cycle days at sessions 1, 2, and 4, and for minutes to stage 2 sleep at sessions 1 and 2. These effects are shown in Figure 8.

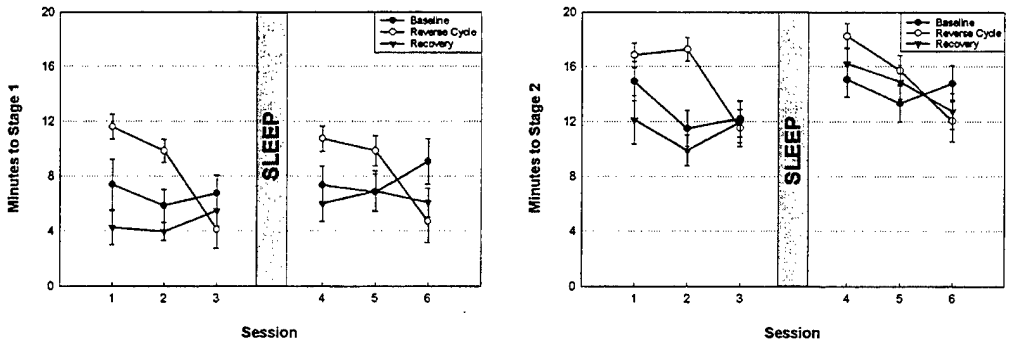

Figure 8. A day by session interaction for latency to stages 1 and 2 from the RTSW.

An interaction between drug group and session occurred for minutes to stage 1 sleep ($F(5,70)=2.45$, $p=.0421$) and minutes to stage 2 sleep ($F(5,70)=2.52$, $p=.0371$). Follow-up analyses indicated a significantly shorter latency to stage 1 for the temazepam group compared to the placebo group at sessions 3 and 5, and at session 5 for minutes to stage 2. These effects are shown in Figure 9.

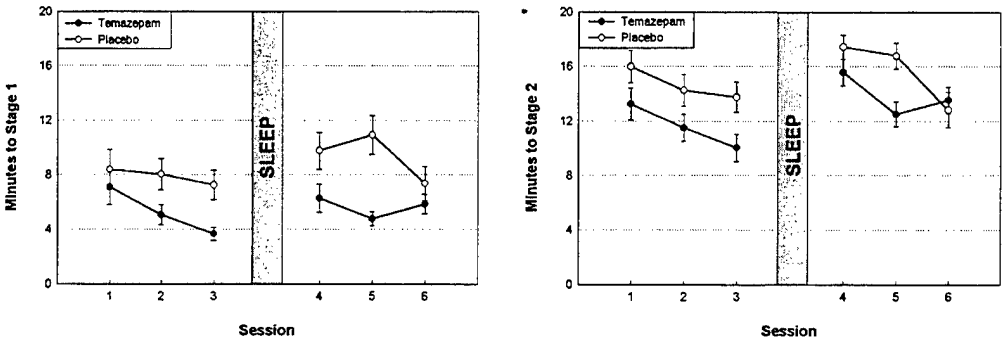

Figure 9. A drug group by session interaction for latency to stages 1 and 2 from the RTSW.

A main effect for drug group occurred for minutes to stage 1 ($F(1,14)=4.77$, $p=.0464$, with a shorter latency to stage 1 for the temazepam group than for the placebo group (means were 5.46 and 8.62, respectively). A main effect for day occurred for minutes to stage 1 sleep ($F(2,28)=5.09$, $p=.0199$) and minutes to stage 2 sleep ($F(2,28)=4.50$, $p=.0202$), with contrasts indicating a significantly shorter latency to stage 1 during the baseline compared to the reverse cycle days; a shorter latency to stage 1 was also found during the reverse cycle compared to the recovery days. The minutes to stage 2 sleep were significantly different only between the reverse cycle and the recovery days, with shorter latency to stage 2 during the recovery days. The means are shown in Table 8.

Table 8.
Means for the main effects for day on the RTSW.

	Minutes to Stage 1	Minutes to Stage 2
Baseline	7.1979	13.6406
Reverse Cycle	8.4802	15.2812
Recovery	5.4427	12.9833

Finally, a main effect for session occurred for minutes to stage 1 sleep ($F(5,70)=3.18$, $p=.0121$) and minutes to stage 2 sleep ($F(5,70)=8.75$, $p=.0371$). Follow-up analyses indicated a significant cubic trend for both minutes to stage 1 and minutes to stage 2 sleep. Table 9 shows the means for this effect.

Table 9.
Means for the main effects for session on the RTSW.

	Minutes to Stage 1	Minutes to Stage 2
Session 1	7.74	14.64
Session 2	6.55	12.89
Session 3	5.46	11.91
Session 4	8.03	16.51
Session 5	7.84	14.66
Session 6	6.61	13.21

Simulator performance

The simulator performance scores from two baseline days, two reverse cycle days, and two recovery days and from the three sessions from each of these days were analyzed with a four-way ANOVA for drug (temazepam and placebo, the grouping factor), day (baseline, reverse cycle, and recovery), session (1000, 1400, and 1800 on baseline and recovery days, and 1800, 2200, and 0200 on reverse cycle days), and, in some cases, iteration (when a maneuver was flown more than once, an additional factor was added). The iteration factor occurred for the three climbs, five straight-and-levels, two descents, and two right descending turns. The other maneuvers were flown only one time per session.

Climb. Analysis of the composite scores from the two climbs was based on how well the participant controlled heading, airspeed, rate of climb, roll, and slip. The ANOVA revealed one

significant effect for iteration ($F(2,28)=99.74$, $p<.0001$), with contrasts among the three climbs indicating that performance on the first climb was significantly lower than performance on the second and third climbs; performance on the second climb was significantly lower than performance on the third climb (means are 64.37, 67.55, and 73.43, respectively).

Straight-and-level (SL). Analysis of the composite scores from the four straight-and-levels was based on how well the participant controlled heading, altitude, airspeed, and roll. The ANOVA revealed a significant iteration effect ($F4,56)=15.34$, $p<.0001$), with contrasts indicating that performance on the first and second SLs were significantly lower than performance on the third, fourth, and fifth SLs; and performance on the fourth SL was significantly higher than performance on the fifth SL (means are 84.91, 83.54, 87.43, 88.07, and 86.76, respectively). There was also a statistically significant day effect ($F(2,28)=13.71$, $p=.0001$) with performance on the baseline days lower than performance on the reverse cycle and recovery days, and performance on the reverse cycle days lower than performance on the recovery days (means are 85.75, 86.39, and 87.29, respectively).

Descent. Analysis of the composite scores from the two descents was based on how well the participant controlled heading, airspeed, rate of descent, roll, and slip. The ANOVA revealed a statistically significant iteration effect ($F(1,14)=14.37$, $p=.0020$), with contrasts indicating that performance on the first descent was better than performance on the second descent (means are 69.63 and 67.43, respectively). A statistically significant effect for day also occurred ($F(2,28)=4.02$, $p=.0293$), with contrasts indicating that performance was lower on the baseline days than on the reverse cycle and recovery days (means are 67.60, 68.83, and 69.17, respectively).

Right standard rate turn (RSRT). Analysis of the composite scores from the RSRT was based on the ability of the participant to control altitude, airspeed, roll, rate of turn, and slip. The ANOVA indicated no significant interactions or main effects for this maneuver.

Right descending turn (RDT). Analysis of the composite scores from the RDT was based on how well the participant controlled airspeed, rate of descent, roll, rate of turn, and slip. The ANOVA indicated a significant interaction among drug group, session, and iteration ($F(5,70)=2.79$, $p=.0234$). The simple effects analysis indicated a significant session by iteration interaction in the temazepam group, but not for the placebo group. Further analyses indicated that a significant quadratic trend occurred for the first RDT, but not for the second. The effects are shown in Figure 10.

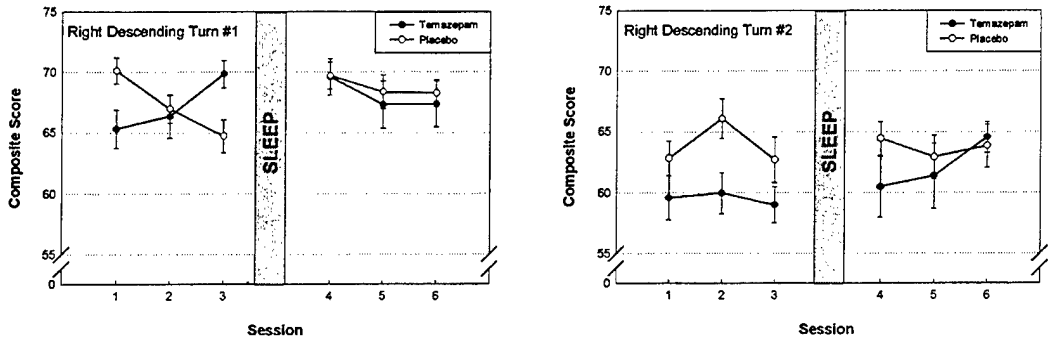

Figure 10. A session by iteration interaction for the RDT.

There was a significant main effect for iteration ($F(1,14)=57.94$, $p<.0001$), indicating that the performance on the first RDT was significantly better than the performance on the second RDT. The means are 67.83 and 62.31, respectively.

Left climbing turn (LCT). Analysis of the composite scores from the LCT was based on how well the participant controlled airspeed, rate of climb, roll, rate of turn, and slip. The ANOVA indicated a statistically significant effect for day ($F(2,28)=9.08$, $p=.0009$). Comparisons among the means found that performance during the baseline days was significantly worse than performance during the reverse cycle and recovery days (means were 57.75, 60.74, and 61.79, respectively).

Right climbing turn (RCT). Analysis of the composite scores from the RCT was based on how well the participant controlled airspeed, rate of climb, roll, rate of turn, and slip. The ANOVA indicated a statistically significant interaction between drug group and day ($F(2,28)=6.63$, $p=.0044$). Follow-up analyses indicated a difference in performance among the days for the temazepam group, but not for the placebo group. Performance for the temazepam group was significantly better on the recovery days than performance on both the baseline and reverse cycle days. The effects are shown in Figure 11.

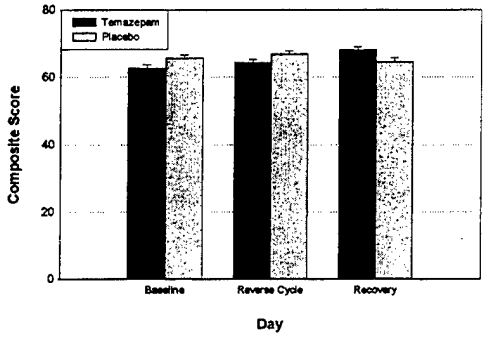

Figure 11. A drug group by day interaction for the RCT.

Left descending turn (LDT). Analysis of the composite scores from the LDT was based on how well the participant controlled airspeed, rate of descent, roll, rate of turn, and slip. The ANOVA indicated no statistically significant interactions or main effects for this maneuver.

ILS approach. Analysis of the composite scores from the ILS was based on how well the participant controlled roll, glide slope, and roll angle. The ANOVA indicated a statistically significant day effect ($F(2,28)=7.32$, $p=.0028$). Contrasts among the means indicated that performance on the baseline days was significantly worse than performance on reverse cycle and recovery days (means are 71.91, 73.95, and 75.72).

Cognitive evaluations

MATB. The four subtasks from the MATB included a communications task, a system monitoring task, a resource management task, and a tracking task. Each of these subtasks were analyzed separately.

The three variables from the communications task were the RT to change the "radio frequency" when instructed, the standard deviation reaction times (SDRTs), and time out (TO) errors or number of times in which no response was made to the instructions to change the radio frequency. The ANOVA for this subtask indicated an interaction between day and session for RT ($F(10,140)=2.15$, $p=.0243$) and TO errors ($F(10,140)=2.34$, $p=.0138$). Scores for RT were higher during the reverse cycle days than during the recovery days at sessions 5 and 6. However, the TO errors were less during the reverse cycle days than during the recovery days at sessions 3, 4, 5, and 6. Finally, the TO errors were less during the baseline days than during the recovery days at sessions 2, 3, 4, 5, and 6. These effects are depicted in Figure 12.

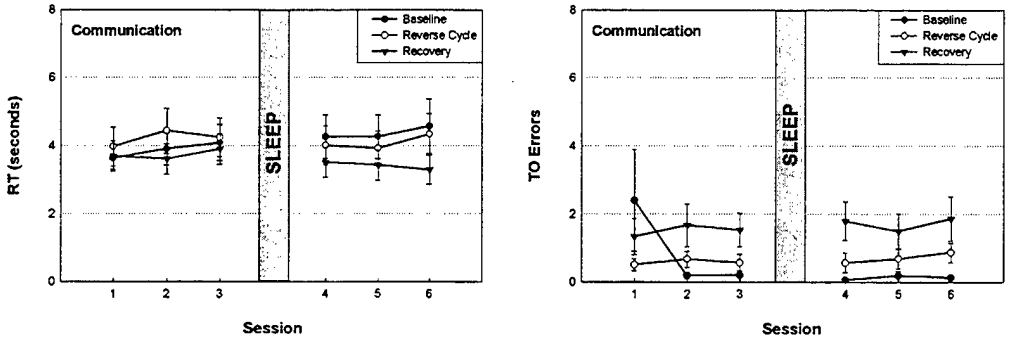

Figure 12. A day by session interaction for RT and TO errors from the MATB.

The resource management task gave a measure of the ability to maintain "fuel levels" in respective tanks at the ideal value of 2500 units. The ANOVA for this task did not reveal any statistically significant difference among the variables.

The systems monitoring task had six variables to analyze. These included RT for lights (how long it took to press one key in response to the onset of a warning light, and to press another key when a different light no longer appeared), the SDRT for lights, RT for dials (how long it took to press a key in response to an out-of-limits excursion of any of four dials), the SDRT for dials, TO errors for lights, and TO errors for dials. The ANOVA revealed a significant session effect for RT for dials ($F(5,70)=3.15$, $p=.0127$), with follow-up analysis indicating a significant linear trend across sessions, decreasing as the sessions progressed. Table 10 shows these effects.

Table 10.
Means for the session main effects for the MATB.

	RT for dials
Session 1	5.30
Session 2	4.98
Session 3	5.00
Session 4	4.30
Session 5	4.54
Session 6	4.46

A significant day effect occurred for RT for dials ($F(2,28)=10.11$, $p=.0005$), SDRT for dials ($F(2,28)= 3.23$, $p=.0548$), TO errors for dials ($F(2,28)=3.30$, $p=.0516$), and SDRT for lights ($F(2,28)= 7.68$, $p= .0022$). Contrasts among the days indicated a significantly longer RT for dials and more variable times as indicated by SDRT during the baseline days than during the reverse cycle days, and a significantly longer RT for dials during the baseline days than during the recovery days. No significant contrasts appeared for SDRT for dials or TO errors for dials. The means are shown in Table 11.

Table 11.
Means for the day main effects for the MATB.

	RT for Dials	SDRT for Dials	TO for Dials	SDRT for Lights
Baseline	5.39	4.16	2.09	1.68
Reverse Cycle	4.60	3.76	1.62	1.11
Recovery	4.31	3.80	1.41	1.29

The root mean square (RMS) tracking error (the amount of deviation from the cursor target) was analyzed for the tracking task. The ANOVA revealed a significant interaction between day and session ($F(10,140)=4.23$, $p<.0001$) with contrasts indicating significantly higher errors during the

baseline days than during the reverse cycle days at sessions 1, 2, and 5; higher errors during the baseline than during the recovery days at all sessions; and higher errors during the reverse cycle days than during the recovery days at sessions 3 and 6. Figure 13 shows these effects.

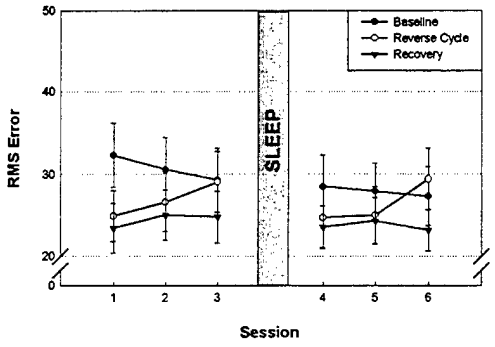

Figure 13. A day by session interaction for RMS tracking errors from the MATB.

A main effect for session occurred ($F(5,70)=3.13$, $p=.0131$) with follow-up analyses indicating a significant cubic trend (see Table 12). A main effect for day occurred as well ($F(2,28)=10.49$, $p=.0004$). Contrasts analyses indicated significantly more errors during the baseline than during the reverse cycle and recovery days, and more errors during the reverse cycle days than during the recovery days. The means are 29.34, 26.65, and 24.08 for baseline, reverse cycle, and recovery days, respectively.

Table 12.
Means for the session main effects for RMS errors from the MATB tracking task.

	RT for dials
Session 1	26.90
Session 2	27.44
Session 3	27.74
Session 4	25.62
Session 5	25.77
Session 6	26.66

PVT. RT, reaction time for the slowest 10% responses (RTS), reaction time for the fastest 10% responses (RTF), and the percent of lapses (stimuli to which no response was made) were analyzed with a four-way ANOVA using the factors drug group (temazepam or placebo), day (baseline, reverse cycle, and recovery), session (six sessions across the two days of each day condition), and posture (sitting and standing). One subject's responses throughout the entire study were at least three standard deviations from the other subjects' responses; therefore his data were not included in

the analysis. The number of subjects left for the PVT analysis was 15; the temazepam group had 7 and the placebo group had 8. The analysis initially included a grouping factor for order since the sitting and standing sessions were approximately 2 hours apart. Since no consistent effects were found for this factor, it was not included in the final analysis.

Several statistically significant interactions occurred for the factors. A significant interaction among drug group, day, session, and posture was found for RTF ($F(10,130)=2.12$, $p=.0269$). Follow-up analyses indicated this effect occurred due to a significant difference among the days for the placebo group while in a sitting posture during sessions 1, 3, and 6. The contrasts between each of the days indicated that reaction time was slower during the reverse cycle days compared to the baseline days and recovery days (sessions 3 and 6), and the reaction time during the baseline days was faster than the recovery days during session 3, but slower than the recovery days during session 6. These effects were not evident in the temazepam group. The effects for both drug groups are depicted in Figure 14.

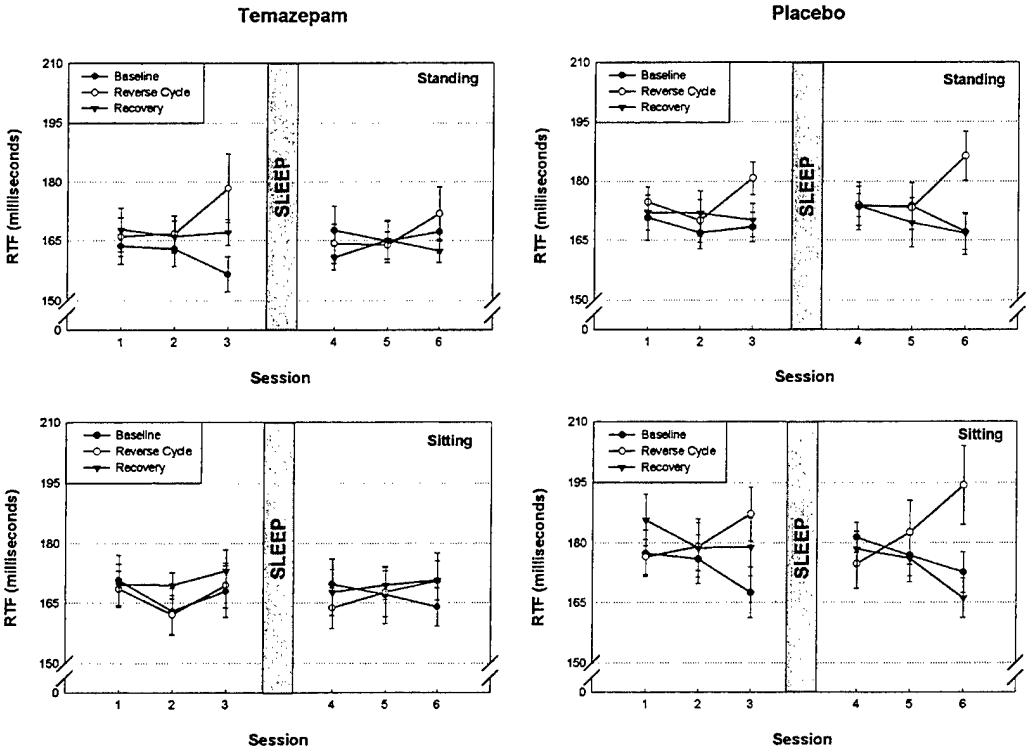

Figure 14. A drug group by day by session by posture interaction for RTF from the POMS.

A statistically significant interaction among drug group, day, and session occurred for RTF ($F(10, 130)=1.94$, $p=.0452$). Follow-up analyses indicated that the temazepam group had significantly faster reaction times on the baseline days than on the reverse cycle and recovery days

during session 3. The placebo group showed faster reaction times on the baseline and recovery days than on the reverse cycle days during both sessions 3 and 6. These effects are shown in Figure 15.

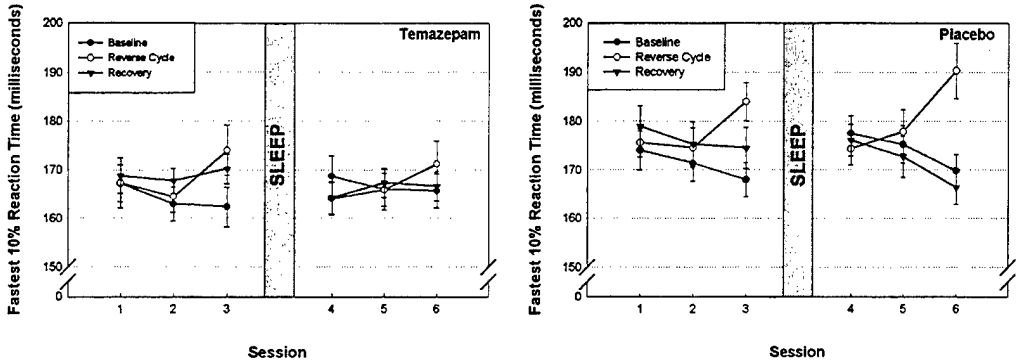

Figure 15. A drug group by day by session interaction for the RTF from the POMS.

A statistically significant interaction between day and posture occurred for RTF ($F(2,26)=3.38$, $p=.0495$). Follow-up analyses indicated this effect was due to faster reaction times on the baseline and recovery days than on the reverse cycle days while subjects were standing, but not while subjects were sitting. These effects are shown in Table 13.

Table 13.
Means for the day by posture interaction for RTF from the PVT task.

	Stand	Sit
Baseline	167.16	171.52
Reverse Cycle	172.80	175.26
Recovery	167.97	173.98

A statistically significant interaction between day and session occurred for RT ($F(10, 130)=3.89$, $p=.0195$), RTF ($F(10,130)=8.53$, $p<.0001$), and percent lapses ($F(10,130)=1.90$, $p=.0507$). Follow-up analyses revealed that the fastest 10% reaction times were slower on the reverse cycle days than on the baseline and recovery cycle days during sessions 3 and 6. In addition, the top 10% reaction times were faster on the baseline days than on the recovery days during session 6. The overall reaction times were slower on the recovery days than on the baseline days and the reverse cycle days during session 1, but reaction times were slower on the reverse cycle and recovery days than the baseline days during session 3. No differences among the days were significant for the percent lapses. These effects are shown in Figure 16.

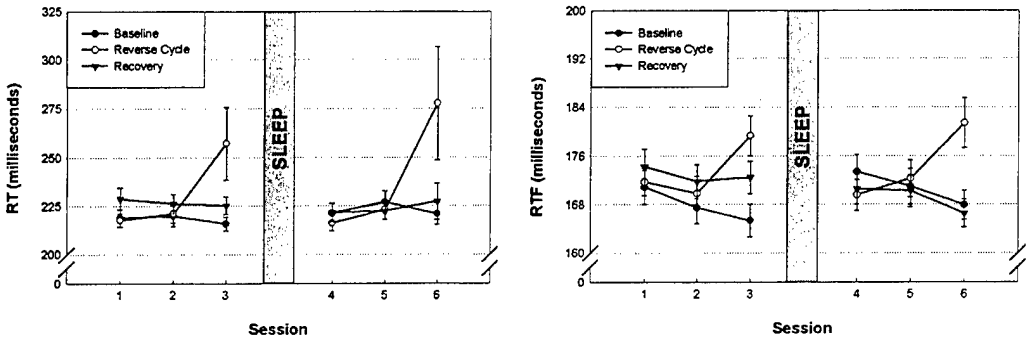

Figure 16. A day by session interaction for RT and RTF from the POMS.

Several main effects occurred along with the higher-order interactions. A significant day effect occurred for RTF ($F(2,26)=3.91$, $p=.0329$). Contrasts between the days indicated that responses were faster during the baseline days than during the reverse cycle days. The effects are shown in Table 14.

Table 14.
Means for the day main effects for RTF from the PVT task.

	RTF
Baseline	169.34
Reverse Cycle	174.03
Recovery	170.98

Finally a significant posture effect occurred for RTF ($F(1,13)=9.92$, $p=.0077$) and percent lapses ($F(1,13)=7.17$, $p=.0190$). As expected, reaction times were faster and lapses were fewer when subjects were standing than when they were sitting. The means for RTF for standing and sitting are 169.31 and 173.59, respectively; the means for percent lapses for standing and sitting are 0.34 and 0.53, respectively.

Waking EEG evaluation

The relative power from the resting eyes open/eyes closed EEG were analyzed for each band of activity (delta, alpha, theta, and beta) using a five-way ANOVA – drug group (temazepam or placebo), day (baseline, reverse cycle, and recovery), session (six sessions on each of the days), posture (sitting and standing), and eyes (open and closed). Since the data are proportions, the two arcsine square-root transformation was implemented as recommended by Winer (1971). Only 3 electrode sites were chosen from the original 21 for analysis because of the presence of recording artifacts. Visual inspection of data from all the sites indicated that EEG activity from Fz, Cz, and Pz were of sufficient quality for further analysis. The analysis initially included a grouping factor for

order since the sitting and standing sessions were approximately 2 hours apart. Since no consistent effects were found for this factor, it was not included in the final analysis.

Delta. Analysis of delta activity (1.5-3.0 hz) revealed several interactions and main effects. The ANOVA indicated an interaction among drug group, day, session, and posture for site Fz ($F(10,140)=1.95$, $p=.0433$). Follow-up analyses indicated that this effect occurred in the temazepam group due to a quadratic trend across the session on the recovery day during the standing portion of the EEG; this effect did not occur in the placebo group. This effect is depicted in Figure 17.

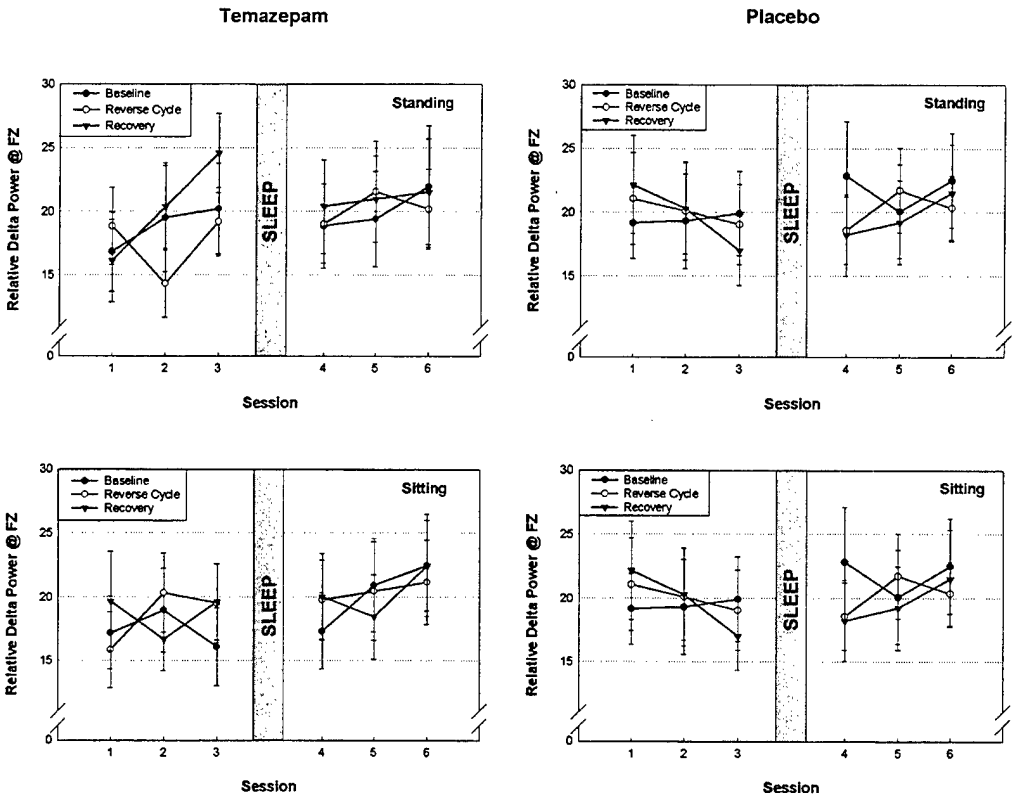

Figure 17. A drug group by day by session by posture interaction from site Fz for delta activity.

Several three-way interactions occurred among the variables. A effect among drug group, day, and posture occurred for site Fz ($F(2,28)=3.51$, $p=.0438$), due to more delta activity for the placebo group on the recovery day than on the baseline and reverse cycle days; this effect did not occur for the temazepam group. This effect is shown in Figure 18.

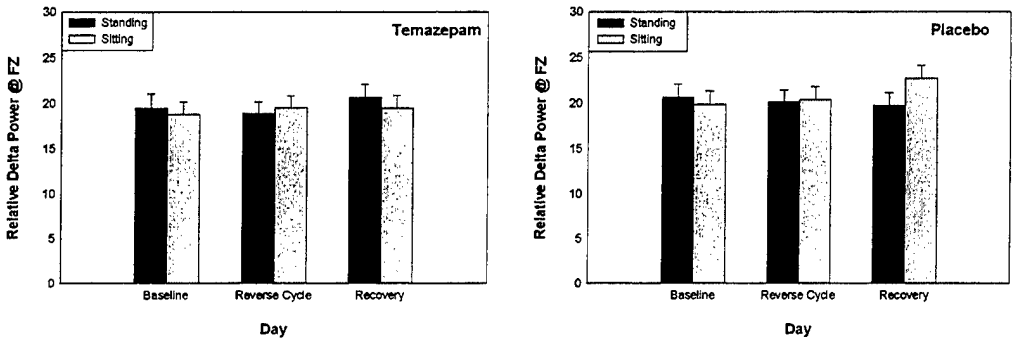

Figure 18. A drug group by day by posture interaction from site Fz for delta activity.

Another three-way interaction occurred among day, session and eyes at site Fz ($F(10,140)=2.15$, $p=.0242$). Follow-up analyses indicated this interaction occurred due to a linear increase in delta activity as the sessions progressed when the eyes were open, but not when eyes were closed, during the reverse cycle day. No other days showed this trend. These effects are depicted in Figure 19.

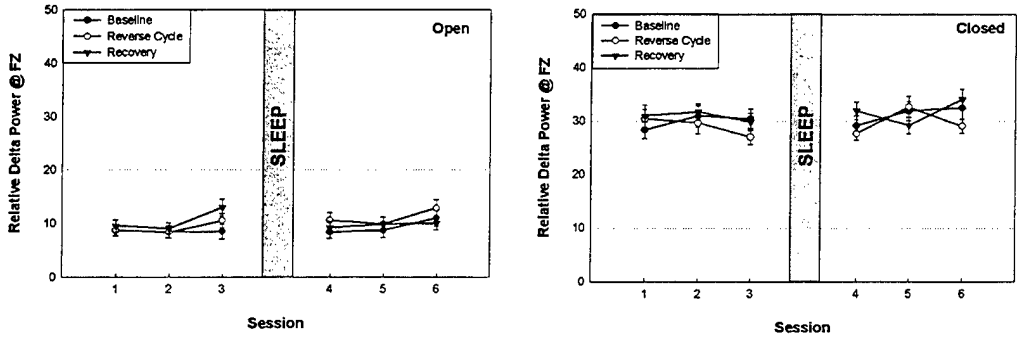

Figure 19. A day by session by eyes interaction from site Fz for delta activity.

Among the two-way interactions which occurred was between drug group and session at site Fz ($F(5,70)=2.41$, $p=.0446$). Follow-up analyses indicated a linear trend in the sessions for the temazepam group, but not for the placebo group ($p=.0563$). This effect is shown in Figure 20.

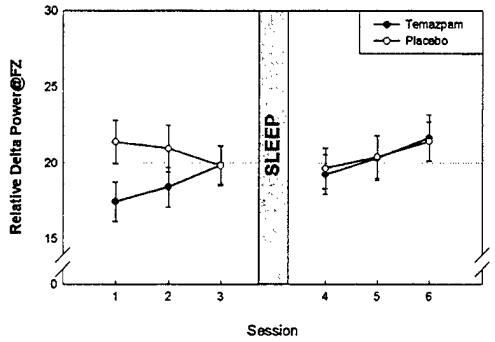

Figure 20. A drug group by session interaction from site Fz for delta activity.

Another two-way interaction occurred for day and posture at site Pz ($F(2,28)=3.38$, $p=.0486$) due to more delta activity while sitting than while standing on the recovery day which did not occur on the baseline and reverse cycle days. This effect is shown in Table 15.

Table 15.
Means for the day by posture interaction at site Pz for delta activity.

	Stand	Sit
Baseline	16.5214	15.8516
Reverse Cycle	15.6845	15.8225
Recovery	16.4767	17.8907

An interaction between day and eyes occurred for site Cz ($F(2,28)=5.62$, $p=.0088$) due to less delta activity during baseline than during the reverse cycle or recovery days during eyes open, but not during eyes closed. There was less delta activity during the reverse cycle days than during the recovery days during eyes open. These effects are shown in Table 16.

Table 16.
Means for the day by eyes interaction at site Pz for delta activity.

	Open	Closed
Baseline	8.8636	30.2030
Reverse Cycle	10.0151	28.0657
Recovery	11.1735	29.8845

Finally, an interaction between session and eyes occurred at sites Cz ($F(5,70)=2.73$, $p=.0262$) and Fz ($F(5,70)=2.83$, $p=.0221$). This interaction occurred because of linear and cubic trends at eyes open, but not at eyes closed. Figure 21 shows this effect.

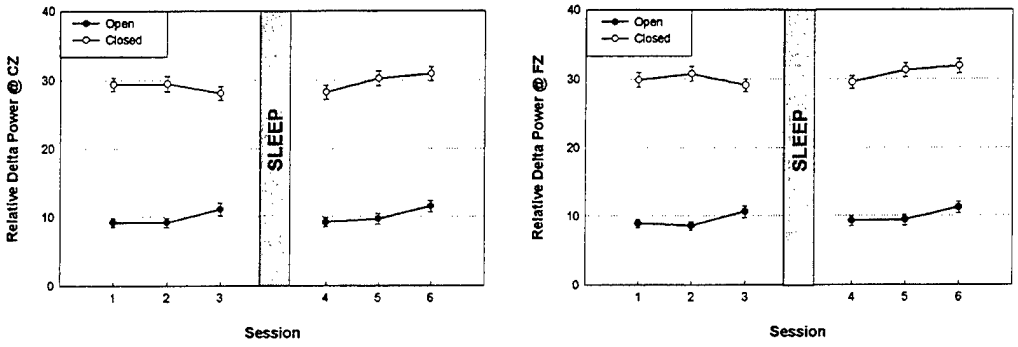

Figure 21. A session by eyes interaction from sites Cz and Fz for delta activity.

A main effect for session occurred at sites Cz ($F(5,70)=3.20$, $p=.0117$) and Fz ($F(5,70)=2.51$, $p=.0381$). There was a significant quadratic trend at Cz (Fz was not significant) as shown in Table 17.

Table 17.
Means for the main effect for session at sites Cz and Fz for delta activity.

	Cz	Fz
Session 1	19.32	19.42
Session 2	19.33	19.66
Session 3	19.61	19.85
Session 4	18.75	19.45
Session 5	19.98	20.36
Session 6	21.23	21.55

Finally, a main effect for eyes occurred at sites Cz ($F(1,14)=152.67$, $p<.0001$), Fz ($F(1,14)=198.12$, $p<.0001$), and Pz ($F(1,14)=176.89$, $p<.0001$) due to higher relative delta power when the eyes were closed than when the eyes were opened at each electrode site. The means for this effect are in Table 18.

Table 18.
Means for the main effects for eyes at sites Cz, Fz, and Pz for delta activity.

	Open	Closed
Cz	10.02	29.38
Fz	9.70	30.40
Pz	6.84	25.91

Theta. Analysis of theta activity (3.0-8.0 hz) revealed several interactions among the factors. A drug group by session by posture by eyes interaction occurred at site Cz ($F(5,70)=2.42$, $p=.0439$), however, follow-up analyses did not reveal a significant difference among the means. A significant interaction among drug group, day, posture, and eyes occurred at site Pz ($F(2,28)=3.86$, $p=.0330$) due to more theta activity during eyes open than during eyes closed for the temazepam group while sitting on each of the test days. The effect was not evident during the standing portion of the EEG nor during any of the times for the placebo group. This effect is illustrated in Figure 22.

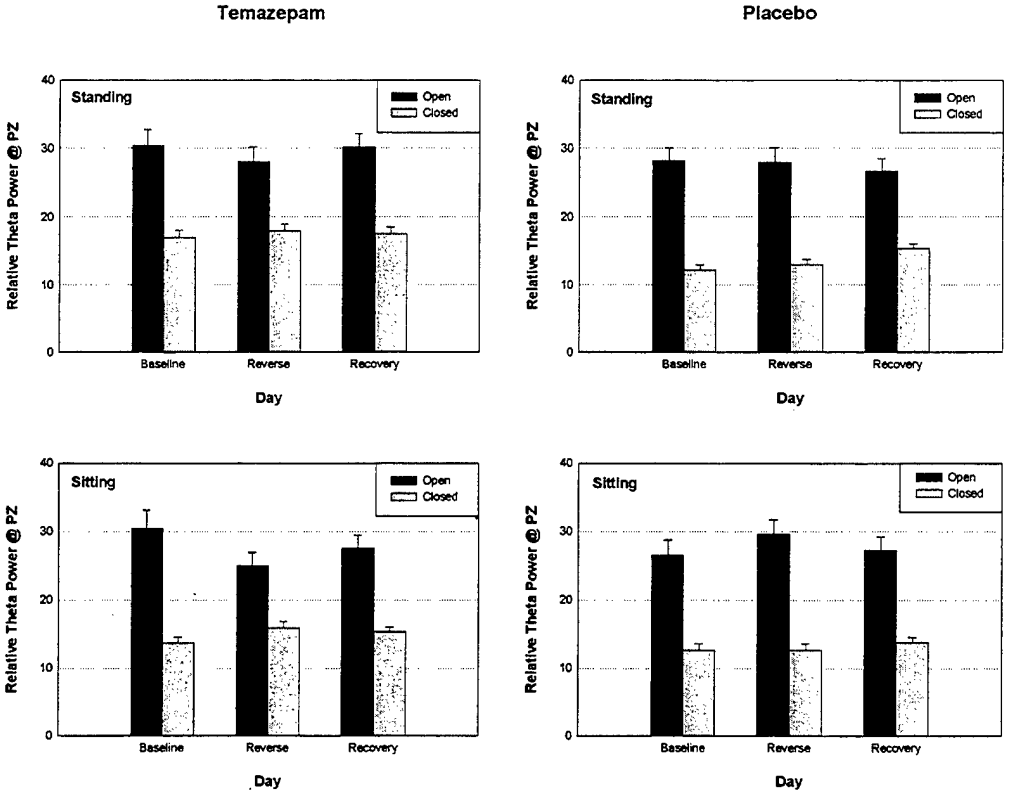

Figure 22. A drug group by session by posture by eyes interaction from site Cz for theta activity.

An interaction among drug group, day, and eyes occurred at sites Cz ($F(2,28)=6.65$, $p=.0043$), Fz ($F2,28)=9.91$, $p=.0006$) and Pz ($F(2,28)=3.56$, $p=.0419$). Follow-up analyses did not reveal any significant differences among the means.

In addition to the interactions, a main effect for eyes occurred at sites Cz ($F(1,14)=31.23$, $p<.0001$), Fz ($F(1,14)=31.15$, $p<.0001$), and Pz ($F(1,14)=25.35$, $p=.0002$) due to more relative theta power during eyes open than during eyes closed.

Alpha. Analysis of alpha activity (8.0-13.0 hz) showed several interactions and main effects. A three-way interaction occurred among drug group, day, and session at site Cz ($F(10,140)=2.15$, p.0244) due to a cubic trend in the sessions during baseline days in the temazepam group, but not in the placebo group. This effect is shown in Figure 23.

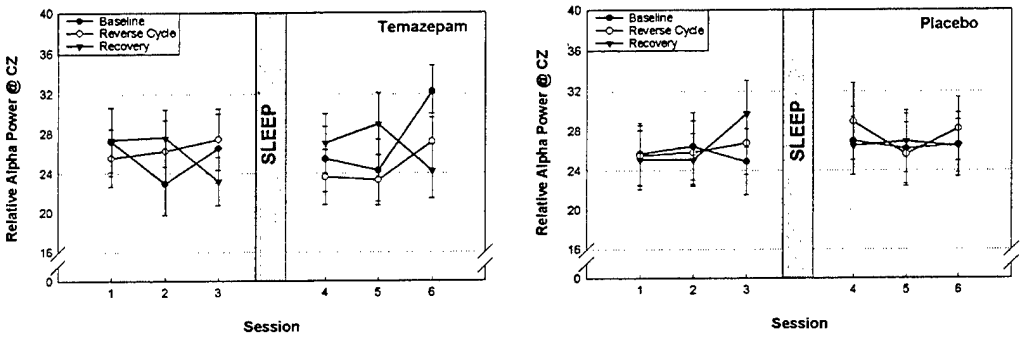

Figure 23. A drug group by day by session interaction from site Cz for alpha activity.

Another interaction occurred among drug group, day, and eyes at site Cz ($F(2,28)=3.30$, $p=.0517$), however, the follow-up analyses did not reveal any significant differences.

An interaction between drug group and posture occurred at site Cz ($F(1,14)=6.03$, $p=.0277$) due to more alpha activity in the temazepam group during the sitting portion of the EEG compared to the standing portion of the EEG. This effect did not occur for the placebo group. This effect is shown in Figure 24.

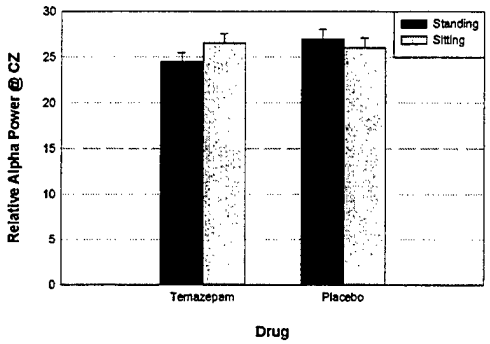

Figure 24. A drug group by posture interaction from site Cz for alpha activity.

Finally, an interaction between day and eyes occurred at sites Cz ($F(2,28)=6.39$, $p=.0052$), Fz ($F(2,28)=7.86$, $p=.0020$), and Pz ($F(2,28)=4.45$, $p=.0211$) due to less relative alpha activity while eyes were open during the baseline day than during the reverse cycle and recovery days at each electrode site (only between baseline and recovery days at Pz). This effect did not occur when eyes were closed. These effects are shown in Figure 25.

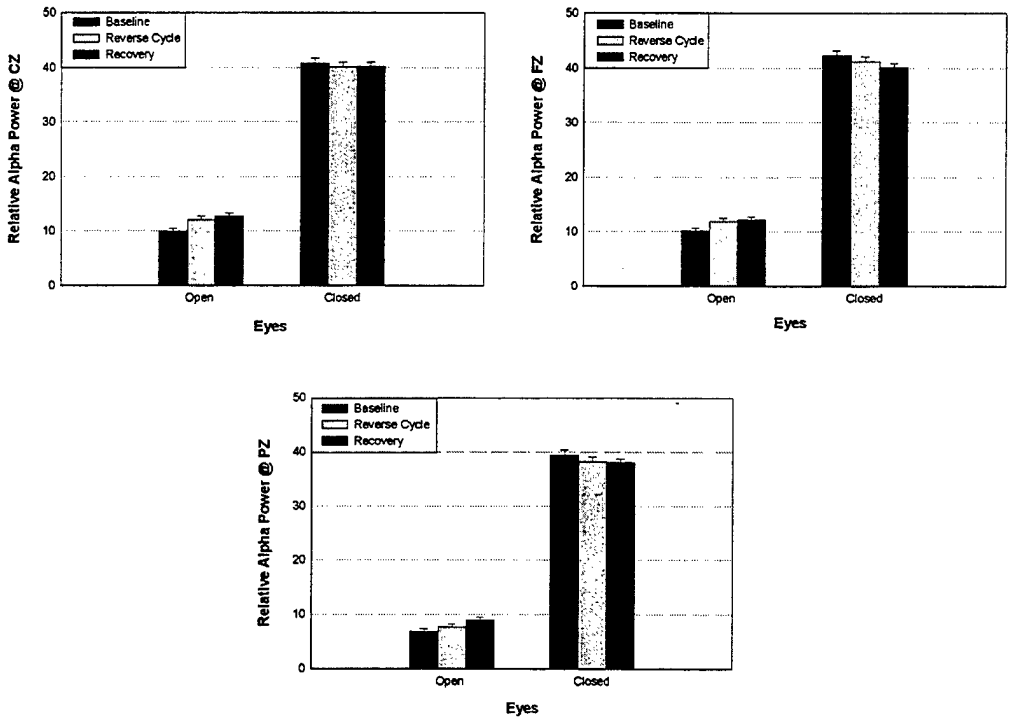

Figure 25. A day by eyes interaction from sites Cz, Fz, and Pz for alpha activity.

There were two significant main effects revealed by this analysis. A main effect for drug group at site Fz ($F(1,14)=4.49$, $p=.0526$) was due to more relative alpha power for the placebo group than for the temazepam group (means are 27.75 and 24.99, respectively). In addition, a main effect for eyes occurred at sites Cz ($F(1,14)=122.20$, $p<.0001$), Fz ($F(1,14)=142.32$, $p<.0001$), and Pz ($F(1,14)=183.83$, $p<.0001$) due to more relative alpha power during eyes closed than during eyes open.

Beta. Analysis of beta activity (13.0-20.0 hz) revealed several interactions and main effects. A significant interaction among drug group, day, posture, and eyes occurred for site Fz ($F(2,28)=6.55$, $p=.0046$) due to more beta activity on the reverse cycle days for the temazepam group while standing with eyes closed than that which occurred for the placebo group. The effects are shown in Figure 26.

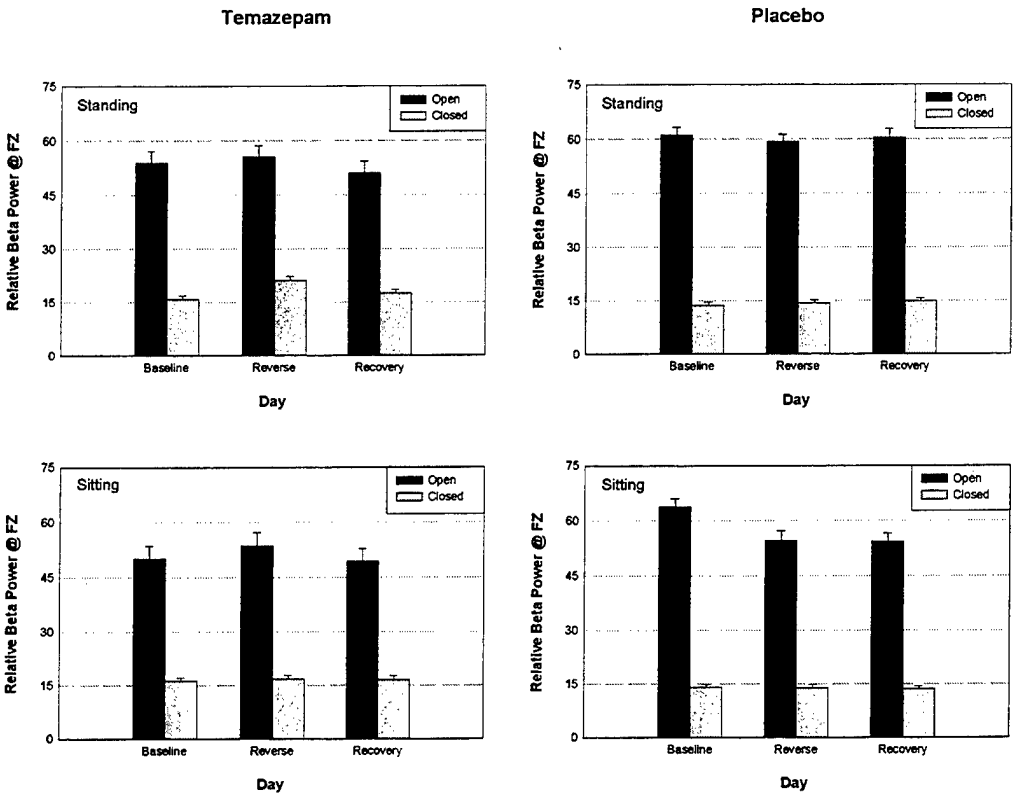

Figure 26. A drug group by day by posture by eyes interaction from site Fz for beta activity.

An interaction among drug group, day, and posture occurred at sites Cz ($F(2,28)=4.55$, $p=.0194$) and Pz ($F(2,28)=5.07$, $p=.0132$), with a tendency at site Fz ($p=.0554$). This effect was due to more beta activity during baseline days than during the recovery days for the placebo group only while sitting, but not for the temazepam group. These effects are depicted in Figure 27.

A final 3-way interaction occurred among day, session, and eyes at site Cz ($F(10,140)=2.54$ $p=.0076$). However, the follow-up analyses did not reveal a significant difference among the means.

A 2-way interaction occurred between day and posture at site Fz ($F(2,28)=4.65$, $p=.0180$) due to more beta activity while standing than while sitting on the reverse cycle and recovery days, but not during the baseline days. The means for each day are shown in Table 19.

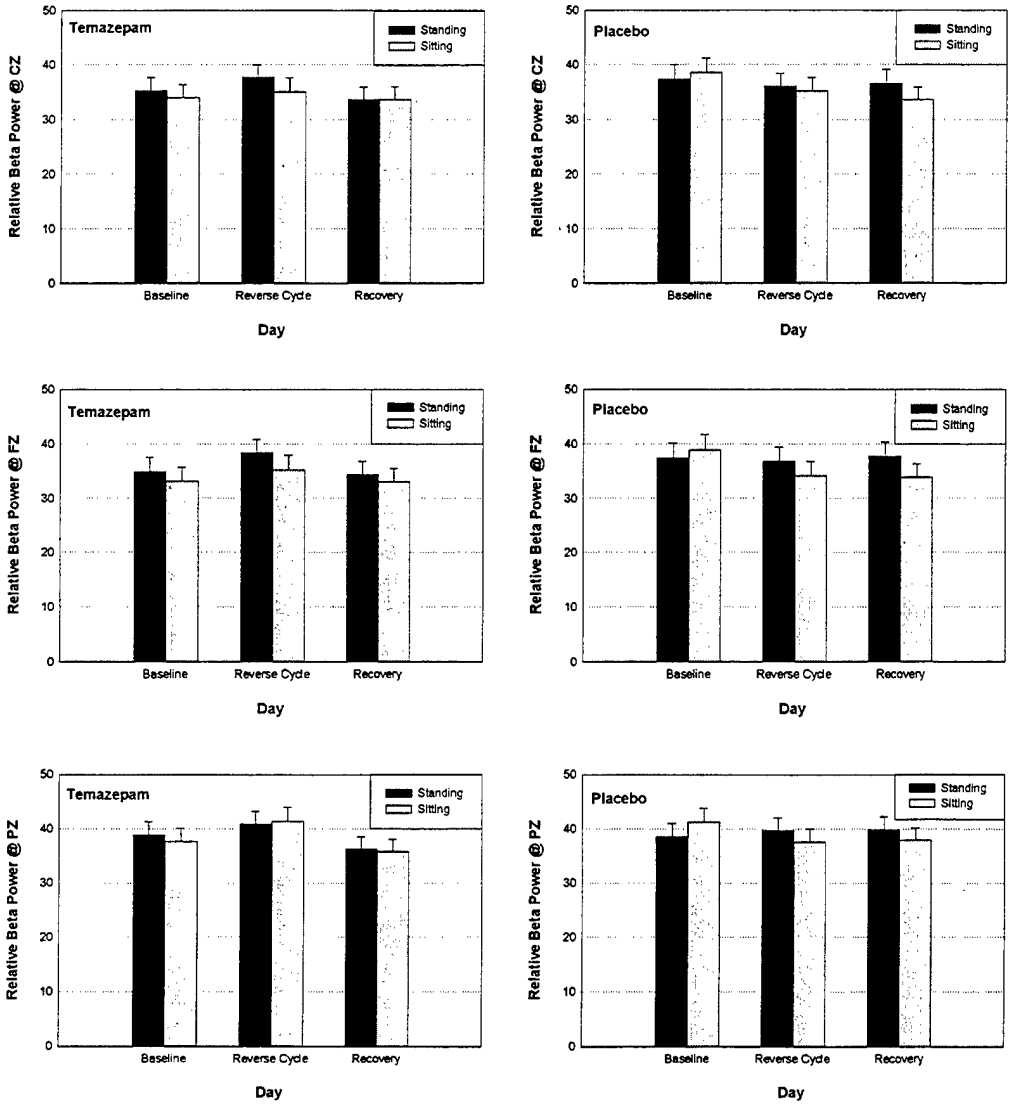

Figure 27. A drug group by day by posture interaction from sites Cz, Fz, and Pz for beta activity.

Table 19.
Means for the day by posture interaction at site Fz for delta activity.

	Stand	Sit
Baseline	20.0729	19.3601
Reverse Cycle	19.5252	19.9752
Recovery	20.2202	21.1277

An interaction between day and eyes occurred at sites Cz ($F(2,28)=6.37$, $p=.0052$) and Fz ($F(2,28)=4.77$, $p=.0165$) due to more beta activity during eyes open than during eyes closed at each of the test days. The interaction occurred because this effect was less apparent on the reverse cycle days than on the other days. The effects are shown in Figure 28.

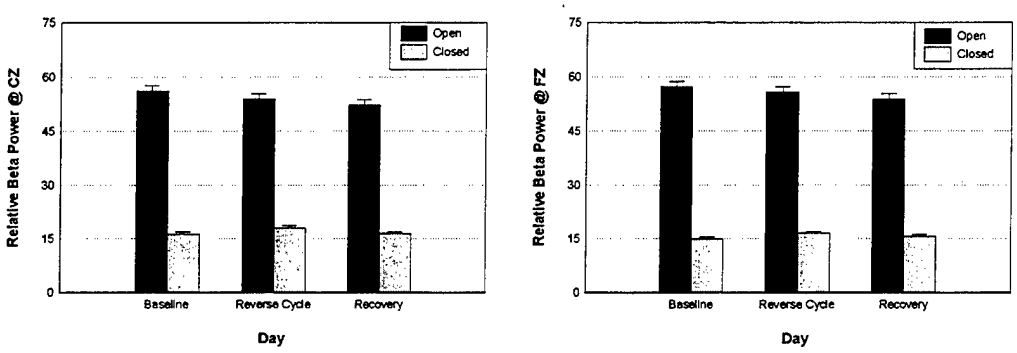

Figure 28. A day by eyes interaction from sites Cz and Fz for beta activity.

A main effect occurred for session at site Fz ($F(5,70)=2.68$, $p=.0282$) due to a linear trend across the sessions, with less beta as time progressed. The means for the sessions are 35.95, 37.81, 35.42, 35.74, 35.42, and 34.11, respectively. Also, a main effect for eyes occurred at sites Cz ($F(1,14)=99.57$, $p<.0001$), Fz ($F(1,14)=94.99$, $p<.0001$), and Pz ($F(1,14)=173.20$, $p<.0001$) due to more relative beta activity during eyes open than during eyes closed.

Physiological data

The data from the saliva samples included levels of cortisol and melatonin taken every 2 hours while the participant was awake. Core temperature data were recorded every 2 minutes, even when the participant was asleep. The data from the day before the reverse cycle period began and the last day of the reverse cycle period were analyzed to determine if changes occurred in these circadian markers.

Temperature. Core body temperature was collected every 2 minutes via the radio pill each day of the study. The data were reduced to one value every 15 minutes for each day. The peaks of the

curves for day 4 (before the reverse cycle) and day 6 (after reverse cycle) were obtained through visual inspection of the each participant's data. The difference in the peaks was calculated by subtracting the peak time after reverse cycle from the peak time before reverse cycle. These differences were analyzed with a t-test between drug groups and as a difference from 0 for the sample as a whole. No statistically significant changes occurred between the two days for either drug group or the sample as a whole. The temperature curves by drug group for the day before the reverse cycle and the day after the reverse cycle are depicted in Figure 29.

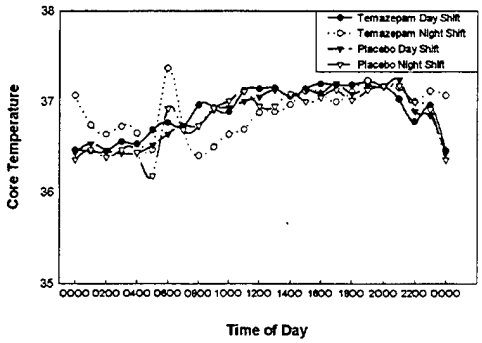

Figure 29. Core body temperature from days 4 and 6 for each drug group.

Hormones. Cortisol and melatonin values were obtained every 2 hours. The peaks of the curves for days 4 and 5 (before the reverse cycle) and for days 6 and 7 (after reverse cycle) were obtained through visual inspection of each participant's data. The difference in the peaks was calculated by subtracting the peak time after the reverse cycle from the peak time before the reverse cycle. The t-test of these peaks indicated no statistical difference between the peak times or between the two drug groups for either the melatonin or cortisol values. The curves by drug group for melatonin and cortisol values before the reverse cycle and after the reverse cycle are shown in Figure 30.

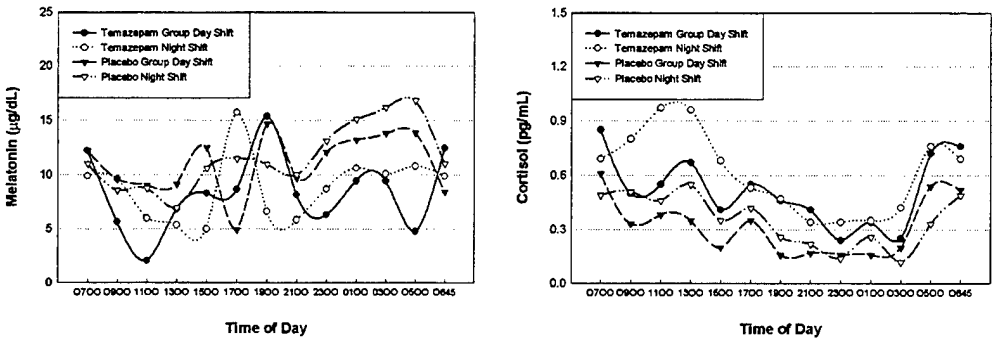

Figure 30. Melatonin and cortisol levels from days 4 and 6 for each drug group.

Polysomnography

The data from the baseline and recovery sleep nights as well as the reverse cycle sleep days were analyzed with a three-way ANOVA using the factors drug group (temazepam and placebo), condition of sleep (baseline vs. reverse cycle vs. recovery), and sleep period (two sleep periods per condition of sleep), with repeated measures on the second and third factors. The variables analyzed consisted of minutes to sleep onset (time from lights out to the first full minute of stage 1 sleep), the number of minutes each person spent in each of the five stages of sleep (stages 1 through 4 and REM sleep), the number of minutes awake after sleep onset (WASO), sleep efficiency (total number of minutes spent in stages 2, 3, 4, and REM divided by total time in bed), REM latency (the time from sleep onset to the first REM period of at least 2 minutes in length), and number of minutes scored as movement time. The sleep efficiency score was converted using the two arcsine square-root transformation to stabilize the variances since these data were expressed in percentages (Winer, 1971). Some participants did not stay in bed the full 8-hour period on the reverse cycle days. When this occurred, only the number of minutes actually spent in bed were used. While some participants did wake early on the reverse cycle sleep periods, they chose to stay in bed awake. For this reason, the number of minutes in each stage is used rather than percent of time spent in each stage in order to capture the shortened time in bed for those who left bed early. Additionally, due to problems in recording the sleep, only the last 10 participants' data were used in this analysis, giving 4 in the placebo group and 6 in the temazepam group.

The ANOVA of the sleep data revealed a two-way interaction between condition of sleep and sleep period for time scored as movement ($F(2,16)=4.78$, $p=.0236$). Simple effects analysis indicated a difference among the conditions on the first reverse cycle sleep period, with movement during the reverse cycle less than the movement on the baseline and recovery sleep nights (means for baseline, reverse cycle, and recovery are 1.15, 0.65, and 1.65, respectively).

An interaction between condition of sleep and drug group also occurred for minutes in stage 2 sleep ($F(2,16)=15.03$, $p=.0002$), minutes in REM sleep ($F(2,16)=10.15$, $p=.014$), minutes awake ($F(2,16)=11.87$, $p=.0003$), and sleep efficiency ($F(2,16)=26.24$, $p<.0001$). Simple effects analysis indicated differences among the drug groups during reverse cycle minutes in stage 2 sleep, minutes awake, and sleep efficiency. The temazepam group showed more minutes in stage 2 sleep, less minutes awake, and higher sleep efficiency than the placebo group. Minutes in REM sleep was not different between the drug groups. The means for each stage of sleep by drug group are shown in Figure 31.

A main effect for condition of sleep occurred in the variable "minutes to sleep onset" ($F(2,16)=25.95$, $p<.0001$), minutes in stage 2 sleep ($F(2,16)=6.61$, $p=.0081$), minutes in REM sleep ($F(2,16)=4.45$, $p=.0291$, WASO ($F(2,16)=8.19$, $p=.0036$), and sleep efficiency ($F(2,16)=8.78$, $p=.0027$). Contrasts between the means indicated a longer sleep onset on the baseline night than on the reverse cycle days and a longer sleep onset on the recovery night than on the reverse cycle days and the baseline nights. Sleep efficiency was better on the baseline nights than on the reverse cycle days, and a tendency to be better during baseline than on the recovery nights ($p=.06$). There were more minutes in stage 2 sleep on the baseline nights than on the reverse cycle days, with a tendency

for more REM sleep on the baseline nights than on the reverse cycle days as well (p=.06). There was more REM sleep on the recovery night than on the reverse cycle days and a tendency for more on the baseline nights than on the reverse cycle days (p=.06). Finally, there was more time awake on the reverse cycle days than on the baseline and recovery nights. These effects are shown in Figure 32.

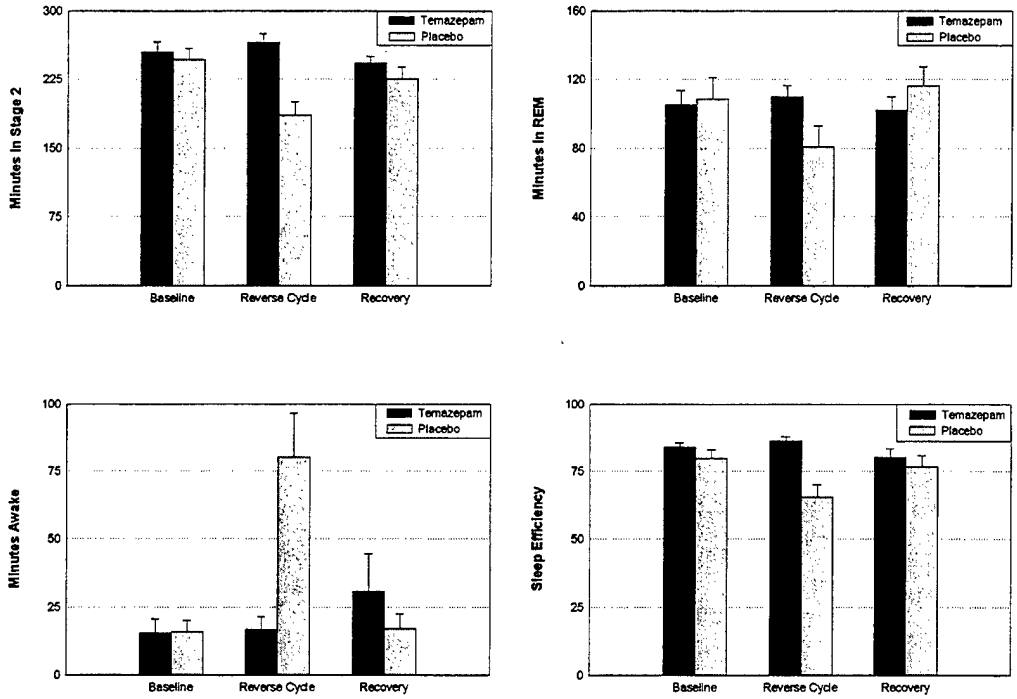

Figure 31. Stages of sleep by day and drug group.

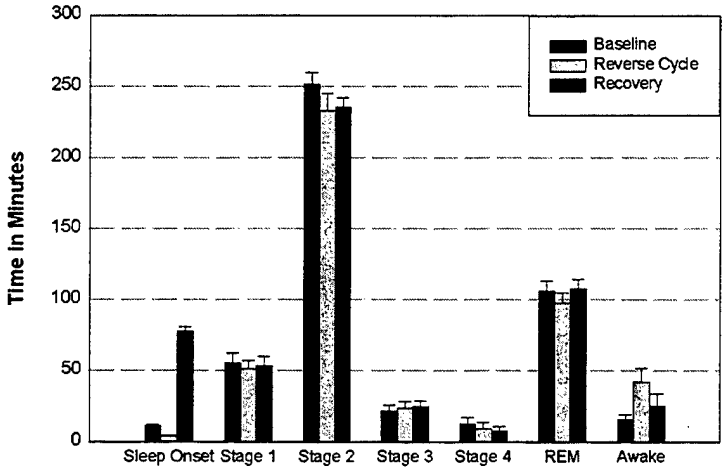

Figure 32. Stages of sleep by day.

Discussion

In general, data from this investigation indicated that temazepam improved daytime sleep and mood over that of placebo, with varying effects on performance. Two groups of aviators were tested to determine whether temazepam would improve their daytime sleep and nighttime performance over three nights on reverse cycle. The effects of improved daytime sleep on subsequent nighttime performance depended on the task, with the vigilance tasks showing some improvement in the temazepam group. The effects on flight performance were not apparent, possibly due to a steady improvement in performance over time. Each task investigated with this study is discussed below.

Mood evaluations

Subjective reports of fatigue, vigor, and confusion from the POMS differentiated the most between the two drug groups. As the night shift progressed into the latter parts of the period, fatigue increased more rapidly in the placebo group than in the temazepam group, especially by the third night shift. Vigor showed the same pattern, with a decrease across the sessions as the night shift progressed. The last evaluation of mood was just before lights out at 0645. Aviators indicated a high level of fatigue and general low mood, especially for those who received placebo. This decrease in general mood is often reported by night workers, with an increase in fatigue as the week on shift progresses (Tilley et al., 1982). While both drug groups in this investigation reported increased fatigue across the nights, this was slightly less in the temazepam group, possibly due to the increase in sleep during the day.

Sleepiness evaluations

The VAS, which measures subjective mood as well as subjective sleepiness, was in agreement with the POMS. Subjective sleepiness increased across the night shifts, with a more rapid increase in the placebo group than in the temazepam group. However, the subjective sleepiness reports did not agree with the objective findings from the RTSWs. Subjects were able to stay awake longer during the reverse cycle nights than during both the baseline days and the recovery days. However, the last session of the night shift showed a greater decline in alertness relative to the baseline and recovery days. Administration of temazepam for improved daytime sleep did not increase objective alertness during the night shift. The temazepam group showed shorter sleep latencies during the naps than the placebo group, however, by the end of the last night shift, this difference between the two drug groups was much smaller. The decrease in sleep latency for the temazepam group could possibly be linked to hang-over effects from the temazepam which were not apparent subjectively, but were unmasked when the aviators were placed in a situation where sleep was difficult to avoid.

Simulator performance

Performance continually improved over the test sessions, even during the reverse cycle period, for flight performance. While some decrements were seen across sessions, there was no difference in performance between the two drug groups. One possibility may be that the test sessions did not continue late enough into the morning to capture the low in the circadian rhythm of performance. While subjective mood and sleepiness evaluations continued up until bedtime, simulator performance testing stopped at 0300. Usually, performance decrements in highly complex tasks such as flying a helicopter are picked up during the circadian trough which occurs about 0500. Since this protocol was simulating a typical night shift for aviators, then the flights were completed by early morning, which is the standard scheduling of reverse cycles (Caldwell et al., 1999), and therefore not during the traditional circadian low in performance.

Cognitive evaluations

The MATB subtasks tended to show a decrement during the reverse cycle period compared to the baseline days. This became noticeable for the standard deviations in the reaction times, showing that the variability in performance was higher during the reverse cycle period than during the baseline and recovery periods. While the reaction times were not affected greatly by reverse cycle, the ability of aviators to maintain a constant performance level was. In addition, the vigilance task (PVT) was sensitive to fatigue on the reverse cycle, indicating that tasks which require sustained attention over a period of time are affected in the early morning hours before the final circadian trough. Temazepam appeared to help with the vigilance tasks in that the reaction times were faster and the lapses were fewer for those in the temazepam group than for those in the placebo group. It is possible that sedentary vigilance-type tasks will be improved by better daytime sleep, thereby reducing the effects of the circadian dip in early morning performance.

The countermeasure evaluation of standing versus sitting to enhance alertness indicated that this posture difference is effective in increasing alertness during the early morning hours. During the PVT, lapses were fewer and reaction time was faster when aviators were standing than when they were sitting. This was especially true for the placebo group compared to the temazepam group during the reverse cycle period. The last session of the last night of testing showed slower reaction time while sitting for the placebo group which was not apparent for the temazepam group.

Waking EEG evaluations

The effects which occurred for the EEG were not consistent in regard to the drug group or day. What effects did occur were generally in the fastest band (beta) and the slowest band (delta). On the recovery days, the placebo group exhibited more delta activity than the temazepam group, indicating more sedation at this time than at other times. However, the temazepam group, in general, showed more delta activity than the placebo group when days were collapsed. Beta activity was higher on the reverse cycle days for the temazepam group than for the placebo group, indicating more alertness for this group during these days. It appears that, in general, temazepam helped increase alertness on the reverse cycle nights compared to placebo.

In addition, it appears that delta activity was higher and beta activity was lower when subjects were sitting than when standing. Also, alpha activity was higher when eyes were closed than when they were open. Both these effects with posture and eyes were expected based on past research.

Physiological data

Although the temazepam group had better daytime sleep than the placebo group, they did not have faster adaptation to reverse cycle. There was little evidence that better daytime sleep should have a significant impact on adaptation to night shift over such a short time.

Polysomnography

As expected, temazepam significantly improved daytime sleep over placebo. The sleep was more consolidated, with less time awake and better sleep efficiency with a medium-acting hypnotic. The ability to remain asleep through most of the 8-hour sleep period led to improved mood over the night shift, which is significant when an aviator is having to work with others. Feeling better during a shift can improve morale and keep communication with other crew members high, which in turn, may help improve alertness through the early morning hours.

Summary and conclusions

Temazepam was successful in improving daytime sleep compared to placebo. Subjects in the temazepam group slept longer and with less fragmentation than those subjects in the placebo group. Generally, the subjects in the temazepam group indicated more subjective alertness and less fatigue than those subjects in the placebo group, as measured by questionnaire and the vigilance task (PVT). However, the objective measure of alertness, the RTSW, indicated higher sleepiness levels in the temazepam group than in the placebo group. The temazepam may have residual effects during the night such that when people are placed in an environment which is highly conducive to sleep, the ability to fight drowsiness is not strong enough to prevent sleep from occurring. Flight performance was not affected by improved daytime sleep, possibly due to the early time of the last flight. If testing had continued into the later morning hours, more effects may have been evident for the flight. Physiologically, the circadian rhythm was not altered in this short time span, regardless of the quality or quantity of sleep which occurred during the day. However, fatigue was more evident on the recovery days for the placebo group when compared to the temazepam group. This information is important since it would appear that the cumulative fatigue occurred more slowly for those who had better daytime sleep than for those who were less restful.

The use of temazepam as a countermeasure for attenuating the fatigue which occurs when people are required to work nights and sleep during the day is beneficial in many ways. Daytime sleep is more consolidated and longer, which leads to better mood over the night. Some tasks are improved by the increased alertness; simple reaction time and vigilance were improved in this study. However, other tasks did not show improvement – simulator flights – and objective alertness was not improved with better daytime sleep. This effect may have occurred due to the residual

effects of temazepam. Taking into account the mixed results of using this hypnotic for daytime sleep, one should be careful and weigh all the issues before determining the best countermeasure for helping improve alertness on the night shift.

References

Åkerstedt, T. 1988. Sleepiness as a consequence of shift work. *Sleep*, 11(1): 17-34.

Åkerstedt, T., and Gillberg, M. 1982. Displacement of the sleep period and sleep deprivation. *Human Neurobiology*, 1: 163-171.

Allen, R. P., Mendels, J., Nevins, D. B., Chernik, D. A., and Hoddes, E. 1987. Efficacy without tolerance or rebound insomnia for midazolam and temazepam after use for one to three months. *Journal of clinical Pharmacology*, 27: 768-775.

American Sleep Disorders Association. 1994. *Coping with shift work.* Rochester, MN.

Brainard, G.C., Rollag, M.D., and Hanifin, J.P. 1997. Photic regulation of melatonin in humans: ocular and neural signal transduction. *Journal of Biological Rhythms*, 12(6):537-546.

Breimer, D. D. 1979. Pharmacokinetics and metabolism of various benzodiazepines used as hypnotics. *British Journal of Pharmacology*, 8: 7S-13S.

Caldwell, J. L., Gilreath, S. R., and Norman, D. N. 1999. *A survey of work and sleep hours of U.S. army aviation personnel.* USAARL Report No. 99-16.

Czeisler, C. A., Johnson, M. P., Duffy, J. F., Brown, E. N., Ronda, J. M., and Kronauer, R. E. 1990. Exposure to bright light and darkness to treat physiologic maladaptation to night work. *The New England Journal of Medicine*, 322(18): 1253-1259.

Dinges, D. F., Pack, F., Williams, K., Gillen, K. A., Powell, J. W., Ott, G. E., Aptowicz, C., and Pack. A. I. 1997. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep*, 20(4): 267-277.

Donaldson, E., and Kennaway, D. J. 1991. Effects of temazepam on sleep, performance, and rhythmic 6-sulphatoxymelatonin and cortisol excretion after transmeridian travel. *Aviation, Space, and Environmental Medicine*, 62: 654-660.

Fillingim, J. M. 1979. Double-blind evaluation of the efficacy and safety of temazepam in outpatients with insomnia. *British Journal of clinical Pharmacology*, 8: 73S-77S.

Härmä, M. 1995. Sleepiness and shiftwork: individual differences. *Journal of Sleep Research*, 4(Suppl. 2): 57-61.

Hartse, K. M., Roth, T., and Zorick, F. J. 1982. Daytime sleepiness and daytime wakefulness: The effect of instruction. *Sleep*, 5: S107-S118.

Horne, J. A., and Östberg, O. 1976. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International Journal of Chronobiology*, 4: 97-110.

Kales, A., Bixler, E. O., Soldatos, C. R., Vela-Bueno, A., Jacoby, J. A., and Kales, J. D. 1986. Quazepam and temazepam: effects of short- and intermediate-term use and withdrawal. *Clinical Pharmacology and Therapeutics*, 39: 345-352.

Jones, H., and Higdon, A. 1991. *HAWK data acquisition system users' guide.* USAARL internal working document.

Knauth, P. 1995. Speed and direction of shift rotation. *Journal of Sleep Research*, 4(Suppl. 2): 41-46.

Mattila, M. J., Aranko, K., Mattila, M. E., and Strömberg, C. 1984. Objective and subjective assessment of hangover during subacute administration of temazepam and nitrazepam to healthy subjects. *European Journal of Clinical Pharmacology*, 26: 375-380.

McNair, D. M., Lorr, M., and Droppleman, L. F. 1981. *Manual for the profile of mood states.* San Diego: Educational and Industrial Testing Service.

Minors, D. S., and Waterhouse, J. M. 1990. Circadian rhythms in general. In A. J. Scott (Ed.) *Shiftwork: Occupational Medicine: State of the Art Reviews.* Philadelphia, PA: Hanley & Belfus, Inc., pp. 165-182.

Mitler, M. M., Carskadon, M. A., Phillips, R. L., Sterling, W. R., Zarcone, V. P., Jr., Spiegels, R., Guilleminault, C., and Dement, W. C. 1979. Hypnotic efficacy of temazepam: A long-term sleep laboratory evaluation. *British Journal of clinical Pharmacology*, 8: 63S-68S.

Monk, T. H. 1990. Shifworker performance. In A. J. Scott (Ed.) *Shiftwork: Occupational Medicine: State of the Art Reviews.* Philadelphia, PA: Hanley & Belfus, Inc., pp. 183-198.

Müller, F. O., Van Dyk, M., Hundt, H. K. L., Joubert, A. L., Luus, H. G., Groenewoud, G., and Dunbar, G. C. 1987. Pharmacokinetics of temazepam after day-time and night-time oral administration. *European Journal of Clinical Pharmacology*, 33: 211-214.

Nicholson, A.N. 1979. Performance studies with diazepam and its hydroxylated metabolites. *British Journal of clinical Pharmacology*, 10:39S-42S.

Penetar, D., McCann, U., Thorne, D., Kamimori, G., Galinski, C., Sing, H., Thomas, M., and Belenky, G. 1993. Caffeine reversal of sleep deprivation effects on alertness and mood. *Psychopharmacology*, 112: 359-365.

Penn, P. E., and Bootzin, R. R. 1990. Behavioral techniques for enhancing alertness and performance in shift work. *Work & Stress*, 4(3): 213-226.

Physicians' Desk Reference. 2000. Restoril. Montvale, NJ: Medical Economics Company, Inc. pp 1894-1896.

Porcù, S., Bellatreccia, A., Ferrara, M., and Casagrande, M. 1997. Performance, ability to stay a wake, and tendency to fall asleep during the night after a diurnal sleep with temazepam or placebo. *Sleep*, 20(7): 535-541.

Rechtschaffen, A., and Kales, A. 1968. *A Manual of Standardized Terminology: Techniques and Scoring System for Sleep Stages of Human Subjects*. Los Angeles: UCLA Brain Information Service/Brain Research Institute.

Roth, T., Piccione, P., Salis, P., Kramer, M., and Kaffeman, M. 1979. Effects of temazepam, flurazepam and quinalbarbitone on sleep: Psychomotor and cognitive function. *British Journal of clinical Pharmacology*, 8: 47S-54S.

Roth, T., and Roehrs, T. A. 1991. A review of the safety profiles of benzodiazepine hypnotics. *Journal of Clinical Psychiatry*, 52(9, Suppl.): 38-41.

Scharf, M. B., Fletcher, K., Graham, J. P. 1988. Comparative amnestic effects of benzodiazepine hypnotic agents. *Journal of Clinical Psychiatry*, 49(4): 134-137.

Schwarz, H. J. 1979. Pharmacokinetics and metabolism of temazepam in man and several animal species. *British Journal of clinical Pharmacology*, 8: 23S-29S.

Stone, B. M., and Turner, C. 1997. Promoting sleep in shiftworkers and intercontinental travelers. *Chronobiology International*, 14(2): 133-143.

Tilley, A. J., Wilkinson, R. T., Warren, P. S. G., Watson, B., and Drud, M. 1982. The sleep and performance of shift workers. *Human Factors*, 24(6): 629-641.

Vidaček, S., Kaliterna, L., Radošević-Vidaček, B., and Folkard, S. 1986. Productivity on a weekly rotating shift system: Circadian adjustment and sleep deprivation effects? *Ergonomics*, 29(12): 1583-1590.

Wesnes, K., and Warburton, D. M. 1984. A comparison of temazepam and flurazepam in terms of sleep quality and residual changes in performance. *Neuropsychobiology*, 11: 255-259.

Wesnes, K., and Warburton, D. M. 1986. Effects of temazepam on sleep quality and subsequent mental efficiency under normal sleeping conditions and following delayed sleep onset. *Neuropsychobiology*, 15: 187-191.

Winer, B.J. 1971. *Statistical principles in experimental design*. New York: McGraw-Hill Book Co.

Appendix A.

Sleep diary.

USAARL SLEEP LOG

Example Sleep Log

Fill out when you wake up: **Scale: 1=Poor 2=Fair 3=Good** **Fill out before bed:**

Date	Bed time	Approx. time to fall asleep	Number times woke up	Last time you woke up	Time you rose out of bed	TOTAL time in bed	TOTAL time asleep	How well did you sleep last night?	Number of naps taken today?	Approx. length of all naps today
								1 2 3		

NAME _____

Fill out when you wake up: **Scale: 1=Poor 2=Fair 3=Good** **Fill out before bed:**

Date	Bed time	Approx. time to fall asleep	Number times woke up	Last time you woke up	Time you rose out of bed	TOTAL time in bed	TOTAL time asleep	How well did you sleep last night?	Number of naps taken today?	Approx. length of all naps today
								1 2 3		
								1 2 3		
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Appendix B.

Manufacturer's list.

Ambulatory Monitoring, Inc.
P.O. Box 609
731 Saw Mill River Road
Ardsley, NY 10502-0609

American Laboratory Products Company (ALPCO)
P.O. Box 451
Windham, NH 03087

Bühlmann Laboratories AG
Postfach
CH – 4123 Allschwil
SWITZERLAND

Cadwell Laboratories
909 North Kellogg Street
Kennewick, WA 99336

Computer Science & Applications, Inc.
2 Clifford Drive
Shalimar, FL 32579

Digital Equipment Corp.
P.O. Box C52008
Nashua, NH 03061-2008

Grass Instrument Co.
101 Old Colony Ave.
Quincy, MA 02169

Milenia Biotec GmbH
Hohe Straße 4-8
61231 Bad Nauheim
GERMANY

Tecan U.S. Inc.
P.O. Box 13953
Research Triangle Park, NC 27709